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PhD THESIS

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EMERGENCY GASTROINTESTINAL SURGERY – PERIOPERATIVE FLUID BALANCE, POSTOPERATIVE COMPLICATIONS, AND DEATH

Cohort studies and initiation of a multicentre randomised clinical trial

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“Poison is in everything,
and no thing is without poison.
The dosage makes it either
a poison or a remedy.”
Paracelsus

PhD Thesis

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Preface

This PhD thesis is based on studies carried out between 2015 and 2019 during my time as a PhD student at the Department of Surgery, Holbæk Hospital. Included are two retrospective cohort studies and one prospective cohort study based on data from a randomised clinical trial of which the protocol is presented.

The retrospective cohort studies were conducted as a teamwork between physicians at Holbæk, Slagelse, and Køge Hospitals. The objective was to study the association between the fluid balance during emergency gastrointestinal surgery and complications, and the association between complications and death following emergency gastrointestinal surgery. The studies were planned, conducted, and completed by the author of this thesis.

In 2015 the randomised clinical trial 'Goal-directed fluid therapy in urgent Gastrointestinal Surgery – A Randomised multicentre Trial: The GAS-ART trial' was initiated as a collaboration between anaesthetists and surgeons at Herlev, Holbæk, Odense, Slagelse, and Svendborg Hospitals. The idea behind the GAS-ART trial was developed by Birgitte Brandstrup, who also drafted the protocol. The protocol was refined through the teamwork of physicians working behind the GAS-ART trial. The project was led by MD, Anders Voldby. The aim of the GAS-ART trial was to investigate whether a zero-balance goal-directed fluid therapy compared with a standard fluid regimen reduced postoperative complications following emergency surgery for gastrointestinal obstruction or perforation. More than 20 doctors worked as dedicated team members in the GAS-ART group. Due to the slow inclusion rate, the GAS-ART trial was handed over to MD, Anne Aaen during the spring of 2017. Patient inclusion and follow-up was completed in November 2018. Preliminary results revealed no difference in the primary outcome and that the perioperative fluid administration was comparable between the allocated arms.

The prospective cohort study is a re-assessment of the data from the GAS-ART trial evaluating the association between perioperative fluid balance and postoperative complications in the entire study population.

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Last my utmost gratitude to my family: My beloved wife Christel for your outstanding support and caring dialogues. Life with you is a wonderful adventure. My deepest thankfulness for bearing with me when work overtook free time, weekends, and holidays. Our three wonderful kids Storm, Bjørg, and Vilja for playing, laughing, and reminding me of the essence of life. My parents, Signe and Kim, for standing by our side through the juggling of work and life. My parents-in-law, Margrethe and Nicolai for caring for our kids and letting my wife and I dance. A big thanks to my siblings Katrine, Christian, and Hans for encouraging support. My deep appreciation goes to Christian, Thomas, and Margrethe for valuable feedback on scientific matters in the thesis.

Anders Winther Voldby,
August 2020

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English Summary

More than 310 million people undergo major surgery every year. One of ten are considered high-risk patients, but they account for approximately 80 percent of the deaths. Patients undergoing emergency gastrointestinal surgery are faced with some of the most unfavourable outcomes. Approximately half of the patients develop major postoperative complications, and one of four are dead after 90 days. Intravenous fluid administration is an incorporated part of perioperative care and is given to replace fluid losses, ensure a sufficient circulation of organs, and safeguard plasma constitution. Hypovolemia may lead to organ impairment and failure. Therefore, liberal intravenous fluid administration has been given during surgery with reported body weight gain of 5–10 kg. However, fluid overload is associated with an increased risk of complications. The aim of this PhD thesis is to study the association between perioperative fluid balance, complications, and death following emergency surgery for gastrointestinal obstruction or perforation.

We set forth to test whether a liberal fluid administration was associated with an increased risk of various postoperative complications in accordance with findings in studies of patients undergoing planned surgery. We found a perioperative fluid balance above 2.5 L to be associated with an increased risk of cardiopulmonary complications following emergency gastrointestinal surgery. Further, we found a potential perioperative fluid balance optimum between 0–2 L. We tested that hypothesis in the second cohort study and found a perioperative fluid balance above 2.0 L to be associated with an increased risk of cardiopulmonary complications. A negative fluid balance was not associated with the risk of complications. Both studies showed that cardiopulmonary and renal complications were associated unevenly with the perioperative fluid balance. Finally, we investigated how various complications were associated with death and found in the adjusted analysis that atrial fibrillation, deep wound complications, and respiratory failure were most strongly related with death. Atrial fibrillation was the only complication associated with death in subgroups of patients with gastrointestinal obstruction or perforation.

The studies show that a perioperative fluid balance below 2–2.5 L during emergency gastrointestinal surgery may have the potential to improve the risk of postoperative cardiopulmonary complications and that atrial fibrillation and respiratory failure are strongly associated with death. Future studies are urged to address the effect of perioperative fluid optimisation during emergency abdominal surgery in a randomised setup to explore the causal relations on this subject. Future studies are also encouraged to investigate the uneven associations between perioperative fluid balance and cardiopulmonary or renal complications and an optimised treatment for weeks after the initial surgical procedure.

Dansk resumé

Mere end 310 millioner mennesker får årligt foretaget større kirurgiske indgreb. En ud af ti betragtes som høj-risiko patienter, og udgør omkring 80% af dødsfaldene. Forløbet efter akut gastrointestinal kirurgi er blandt de mest ufordelagtige. Omkring halvdelen af patienterne udvikler alvorlige postoperative komplikationer, og hver fjerde afgår ved døden inden for 90 dage. Intravenøs væskebehandling er en integreret del af den perioperative behandling og gives for at erstatte væsketab, sikre en tilstrækkelig cirkulation i organerne og regulere indholdet i plasma. Hypovolæmi kan lede til både organskade og organsvigt. Derfor har man tidligere givet meget intravenøs væske under kirurgi, og vægtstigning på mellem 5-10 kg er blevet rapporteret. På den anden side er for stor væskeindgift også blevet relateret til en øget risiko for komplikationer. Målet med denne PhD afhandling er at undersøge sammenhængen mellem perioperativ væsketerapi, komplikationer og død efter akut operation for tarmslyng eller tarmperforation.

Vores mål var at undersøge, om en stor væske administration var relateret til øget risiko for forskellige postoperative komplikationer efter akut kirurgi, som det er tilfældet for planlagte kirurgiske patienter. Vores resultater viste, at en perioperativ væskebalance over 2.5L var relateret til en øget risiko for hjerte-lungekomplikationer efter akut gastrointestinal kirurgi. Derudover fandt vi et muligt væskebalance-optimum mellem 0.0 L og 2.0 L. Den hypotese testede vi i det andet kohortestudie, som viste, at en perioperativ væskebalance over 2.0 L var relateret til en øget risiko for hjerte-lungekomplikationer. En negativ væskebalance var derimod ikke relateret til en øget risiko for komplikationer. Begge studier viste, at hjerte-lunge- og nyre-komplikationer var forskelligt relateret til væskebalancen under kirurgi. Til slut undersøgte vi, hvordan forskellige komplikationer var relateret til død, som viste at atrieflimren, dybe sårkomplikationer og vejrtrækningssvigt var stærkest relateret til død i den justerede analyse. Atrieflimren var den eneste komplikation relateret til død både i gruppen af patienter med tarmslyng og tarmperforation.

Studierne viser, at en perioperativ væskebalance under 2.0 L til 2.5 L ved akut mavetarmkirurgi potentielt set kan bedre risikoen for postoperative hjerte-lungekomplikationer, og at atrieflimren og vejrtrækningssvigt er markant relateret til død. Fremtidige studier tilskyndes at udforske effekten af væskeoptimering under akut mavetarmkirurgi i et lodtrækningsstudie for at undersøge årsagsforhold inden for emnet. Desuden tilskyndes fremtidige studier til at undersøge de forskellige relationer mellem den perioperative væskebalance og hjerte-lunge- eller nyrekomplikationer samt en optimeret behandling i uger efter det indledende kirurgiske indgreb.

Abbreviations

ASA	American Society of Anaesthesiologists' Physical Status Classification
CDC	Clavien-Dindo classification
CI	Confidence Interval
ERAS	Enhanced Recovery After Surgery
GDT	Goal-Directed fluid Therapy
GI	Gastro-intestinal
HR	Hazard Ratio
ICD-10	International Classification of Diseases, version 10
ICU	Intensive Care Unit
IQR	Inter Quartile Range
LOS	Length of Hospital Stay
OR	Odds Ratio
PACU	Postanaesthetic Care Unit
POD	Postoperative Day
SOFA	Sequential Organ Failure Assessment score
SV	Stroke Volume

List of papers

Four papers are included in this thesis. Paper I is an observational cohort study of patients undergoing emergency gastrointestinal surgery. Paper II is a prospective study of the cohort from the randomised clinical trial GAS-ART, of patients undergoing emergency gastrointestinal surgery. Paper III is an observational study resembling the cohort in Paper I. Paper IV is the published protocol for the randomised multicentre trial 'GAS-ART'.

Paper I

Peri-operative Fluid Administration and Complications in Emergency Gastrointestinal Surgery – an Observational Study.

Voldby AW, Aaen AA, Loprete R, Eskandarani HA, Boolsen AW, Jønck S, Ekeløf S, Burcharth J, Thygesen LC, Møller AM, Brandstrup B.

Paper II

The Association of the Perioperative Fluid Balance and Cardiopulmonary Complications in Emergency Gastrointestinal Surgery – A Re-assessment of a Randomized Trial

Voldby AW, Aaen AA, Møller AM, Brandstrup B.

Paper III

Complications and their Association with Mortality Following Emergency Gastrointestinal Surgery – an Observational Study.

Voldby AW, Boolsen AW, Aaen AA, Burcharth J, Ekeløf S, Loprete R, Jønck S, Eskandarani HA, Thygesen LC, Møller AM, Brandstrup B.

Paper IV

Goal-directed fluid therapy in urgent Gastrointestinal Surgery – study protocol for A Randomised multicentre Trial: The GAS-ART trial.

BMJ Open. 2018, 8:11. *Voldby AW, Aaen AA, Møller AM, Brandstrup B*.[1]

1 Background

1.1 Introduction

Today, more than 310 million major surgical procedures are performed each year, and the number is increasing.[2] 'High-risk' patients account for about 10% of the procedures but for approximately 80% of the deaths.[3,4] Patients in need of emergency surgery are often elderly with considerable co-morbidity, and as such are a particularly vulnerable group.[5–7] Emergency gastrointestinal procedures are followed by a risk of postoperative complications of 30%–50% and a mortality risk of 15%–25%. [8–10] The association between postoperative complications and death is strong;[11] however, influenced by co-excising disease, the intraabdominal pathology, and hospital characteristics. Studies are sparse as to which postoperative complications correlate more strongly with death following emergency surgery for gastrointestinal obstruction or perforation.

Patients undergoing emergency surgery diverge in several ways from elective surgical patients. Compromised fluid and food intake as well as vomiting frequently precedes emergency gastrointestinal surgery and skews the fluid homeostasis, which leaves a need for fluid and electrolyte replacement. Additionally, gastrointestinal obstruction or perforation may lead to sepsis[12] enhancing the need for timely fluid administration to avoid organ failure and death.[13–16]

The need for fluid resuscitation of these jeopardized patients is agreed upon. However, the right type, the right amount, and the timing of fluid administration is highly debated, and the clinical practice varies widely.[17,18] For decades, the primary concern has been to avoid unrecognised hypovolemia, which may lead to organ damage and eventually death.[19] Replacement of observed fluid losses but also hypothetical losses led to a liberal perioperative fluid practice[20,21] with little concern about the adverse effects of fluid overload. The kidneys were believed to excrete excess fluid from the administration.[22] Perioperative weight gains of 5–10 kg have been reported.[23,24] However, it takes several days to weeks to excrete a volume overload equivalent to a weight gain of 10 kg.[25]

Fluid overload has been correlated with interstitial oedema formation and increased risk of complications.[22,26] Studies testing a restrictive perioperative fluid regimen compared to a liberal regimen have demonstrated faster gastric emptying, reduced number of complications, and reduced length of hospital stay in patients undergoing elective gastrointestinal surgery.[27–29] Aiming at a perioperative 'zero-balance' with a postoperative bodyweight increase below 1 kg and a fluid balance approximating 0 L, Brandstup and colleagues found a reduced risk of postoperative complications compared with a standard

regimen in patients undergoing elective colorectal surgery.[21] Conversely, an overly restrictive fluid regimen seems to compromise tissue oxygenation and impair renal function following high-risk abdominal surgery.[30,31] Which fluid balance to aim for and how it is associated with various complications is unknown for patients undergoing emergency gastrointestinal surgery.

Timely recognition and handling of events with hypoperfusion is difficult but important to recognise during surgery in high-risk patients.[32] Several strategies have been suggested. Intraoperative fluid optimisation according to flow-related markers (goal-directed fluid therapy, GDT) in elective abdominal surgery has been shown to reduce length of hospital stay and risk of complications compared with standard care.[33–37] High-risk surgical patients in particular seem to benefit from a perioperative GDT.[32,38,39] However, only a pilot study and a terminated randomised trial have addressed perioperative GDT during emergency abdominal surgery with inconsequential clinical relevance.[40,41]

1.2 Objective

The objective of this thesis was to determine the association between perioperative fluid balance and different postoperative complications and to test the association between postoperative complications and death in patients undergoing emergency surgery for gastrointestinal obstruction or perforation. Our hypothesis is that a negative and an overly positive perioperative fluid balance might compromise organ perfusion and increase the risk of postoperative complications. Moreover, we believe that certain postoperative complications correlate unevenly with death and that some complications may serve as clinical markers of patients needing escalation of care. Our aim was investigated through two retrospective cohort studies of patients undergoing emergency surgery for gastrointestinal obstruction or perforation and a prospective cohort study reassessing data from the GAS-ART trial (Goal-directed fluid therapy in urgent Gastrointestinal Surgery – A Randomised multicentre Trial), a randomised clinical multicentre trial comparing two perioperative fluid strategies in patients undergoing emergency surgery for gastrointestinal obstruction or perforation.

1.3 Morbidity and mortality

Emergency abdominal surgery is performed for various indications. Preoperative patient characteristics differ, the intraabdominal pathologies are multiple, and the hospital characteristics are dissimilar. Morbidity and mortality change accordingly.

Patient characteristics

Several patient characteristics are associated with postoperative morbidity and mortality following emergency gastrointestinal surgery. The American Society of Anesthesiologists physical status classification (ASA) or an increasing age have repeatedly been associated with an increased risk of postoperative complications and death.[8,42–44] Further, several comorbidities are linked with postoperative morbidity and mortality of which ischemic heart diseases, pulmonary disease, liver disease, renal disease, or malignancy are highlighted in several studies.[10,45] Additionally, a patient's fitness, expressed as functional status, frailty, or performance score has been documented as an important predictors of the postoperative course.[43,46,47]

The intraabdominal pathology

Morbidity and mortality vary according to intraabdominal pathology and the procedure performed.[7,48] Minor surgical procedures such as appendectomies, cholecystectomies, or endoscopic treatment of gastro-duodenal bleedings have low risk of adverse outcomes but are included in some reports on emergency abdominal procedures.[5,7,43,46,49,50] On the other hand, morbidity and mortality rates are among the highest for patients undergoing major gastrointestinal surgery.[3,11] No national Danish databases provide systematic information on emergency gastrointestinal surgical procedures. The Danish Colorectal Cancer Group registers all surgeries for colorectal cancer and showed a 30-days mortality risk of 15% following emergency surgery.[51] Additionally, the Danish National Indicator Project on patients with perforation or bleeding from gastro-duodenal ulcers show a 30-days mortality risk of 14%–18% and 9% respectively.[52,53]

The Hospital characteristics

National reports from England, USA, and Australia document pronounced variability in postoperative mortality between hospitals after emergency general surgery.[8,54] However, the risk of postoperative complications has been found to be comparable.[55] The metric 'failure to rescue' (death in patients with complications) addresses this matter. Since Silber and colleagues introduced the concept of failure-to-rescue, the metric has been generally accepted and used as a quality marker of hospital performance.[55–57] Delayed recognition of an evolving complication and time to initiate treatment have been associated with an increased risk of complications and death.[4,5,9,58] Additionally, the variability in standard of care and

hospital characteristics including intensive care unit bed capacity, use of radiological diagnostic tools, surgeon volume of procedures, teaching status, or nursing to patient ratio are variables associated with a postoperative outcome.[9,59,60] The concept 'Failure-to-rescue' was, however, originally introduced in elective surgical cases and has only been recently implemented in the area of emergency surgery.[61,62]

1.4 Aspects of Perioperative Fluid Therapy

Perioperative intravenous fluid therapy is given to replace physiological and pathological losses and to maintain or correct the plasma constitution. The variables that need to be considered are the physiological aspects, the pathological aspects, the characteristics of the fluid administered, and the perioperative fluid strategy.

Physiological aspects

Fluid homeostasis in a healthy person is ensured through pressure-related, hormonal, and renal regulation. Approximately 50%–60% of the body weight is water varying according to fat and muscle distribution. The cellular membrane separates the intracellular volume (40%) from the extracellular volume (20%). The extracellular compartment is subdivided into the interstitial compartment (15%) and the intravascular compartment (5%), which are separated by the vascular wall. The vascular wall and cellular membrane determine the distribution of molecules, whereas water moves almost freely across the membranes.[63] The pressure gradient across the vascular wall and the colloid osmotic forces regulate capillary fluid distribution according to Starlings correlation.[64] The vascular wall is freely permeable for small molecules as ions while increased molecular size is gradually restrained and the endothelium is impermeable to proteins.[65]

Pathological aspects

Surgery prompts a hormonal and inflammatory response. The hormonal response prompts fluid retention.[22] However, surgical trauma mediates vasodilation and alters the vascular permeability, which may induce a fluid shift toward the interstitial compartment.[20] Importantly, based on animal trials it seems that oedema in the traumatised tissue increases with additional intravenous fluid infusion.[66] Furthermore, rapid infusion of fluids merits an increase of atrial natriuretic peptide and a potential fluid shift from the intravascular space to the interstitial space.[67]

An adjunct to patients undergoing emergency surgery is sepsis which adds to the inflammatory state. Severe sepsis (grade 3–4) appears in approximately 25% of patients undergoing emergency colorectal surgery.[68] A more severe degree of sepsis is associated with a worse outcome and death.[68] The Surviving

Sepsis Campaign provides international guidelines on how to treat sepsis.[13] Early and ample fluid resuscitation is a key element in treating severe sepsis.

The fluid characteristics

Intravenous administration of isotonic crystalloids is distributed to the entire extracellular volume and the volume expanding effect (intravascular) tends to be short-lived.[69] The intravascular volume expansion of isotonic crystalloids approximates 20%–30% of the fluid volume given after 30 minutes.[70,71] However, the body weight increase corresponds reasonably with the administered volume.[72]

The type of crystalloids administered seems to influence the risk of postoperative complications. Isotonic saline contains 154 mmol/L sodium and chloride; however, the normal serum concentration of chloride is lower (100–110 mmol L^{-1}) and intravenous infusion of isotonic saline might prompt hyperchloremia. Hyperchloremia has been associated with increased length of hospital stay and 30-day mortality.[73] Further, a recent cluster-randomised multicentre crossover trial of patients admitted to the ICU showed increased risk of renal replacement therapy, persistent renal dysfunction, and death in patients treated with saline compared with a balanced crystalloid infusion. [74] It is noteworthy that the relation seemed to be more pronounced in patients with sepsis.

The intravascular volume expanding effect of colloids is greater than that of crystalloids and has been found to exceed the infused volume.[69,75,76] The use of artificial colloids is, however, controversial because hydroxyethyl starch seems to increase the risk of renal replacement therapy and death when used for resuscitation of intensive care patients.[77,78] In alignment, a recent Cochrane review found a slight increase in renal replacement therapy when using starch products compared with various crystalloids for resuscitation in critically ill patients.[79] In comparison, no difference was found between albumin in saline and crystalloids. Likewise, albumin in addition to various types of crystalloid administration compared with crystalloid administration only shows equivalent short-term mortality risk and no significant increase in renal replacement therapy when used for resuscitation in patients with sepsis admitted to the ICU.[80]

Taken together, colloid-based fluid regimens ensure a longer-lasting intravascular volume expanding effect than crystalloids and possess the ability to reduces overall perioperative fluid balance;[81,82] however, the potential adverse effects of artificial colloids need to be considered.

The perioperative fluid strategy

The factors that need to be considered when choosing a perioperative fluid strategy is which fluid to administer, when to give it, and how much is needed. Yet, studies addressing perioperative fluid strategies are generally divided into two groups: studies focusing on replacement of fluid loss by a right amount or studies focusing on the timing of fluid administration.

In clinical practice blood pressure, mean arterial pressure, and heart rate are some of the parameters traditionally used to guide fluid therapy. Heart rate and blood pressure are influenced by many parameters including medicine, anaesthetic drugs, positioning of the patient, blood loss, psychological stress response, and the inflammatory response to surgical stress. It is noteworthy that a blood loss of approximately 15% increases the heart rate modestly and arterial pressure decreases when blood volume is reduced by approximately 30%.[83] However, there is no linear relation between heart rate, arterial blood pressure, and volume loss. As such, these parameters fail to reliably describe the intravascular volume and are incapable of indicating fluid overload.

Diuresis is another variable commonly used when assessing fluid status. Hypovolemia decreases urinary output through an increase in vasopressin. It follows that low diuresis might indicate organ hypoperfusion. However, the invasive surgical procedure in itself prompts an increase in vasopressin, renin-angiotensin, and aldosterone and thereby fluid retention.[22,84] In this manner, a decrease in diuresis is not a reliant indicator of organ hypoperfusion or hypovolemia during surgery.

Fluid volume replacement

Studies on fluid volume replacement are often classified as studies of “restrictive”, “conservative”, “standard”, or “liberal” fluid regimens.[21,27–30,85–88] The nomenclature is challenged by the varying volume of replacement strategies used. A restrictive fluid administration in one study might resemble a liberal regimen in another study.[85,88] The studies compare perioperative fluid strategies based on assumptions about fluid loss combined with measured fluid balance and body weight change. The volume deficit is often calculated from the beginning of fasting prior to surgery. A special concern is the timely handling of occult hypovolemia since fluid-balance and body weight changes are based on retrospective parameters.[31,89]

Studies of Goal-directed fluid therapy

Goal-directed fluid therapy is based on two primary assumptions. Firstly, that the chosen parameter reliably predicts a hypovolemic state. Secondly, that the chosen parameter reliably measures the change of the circulating volume when applying a fluid bolus.

Goal-directed fluid therapy uses predefined aims to guide fluid replacement. Commonly used aims are flow-related variables such as oxygen delivery or estimates of stroke volume. The Frank-Starling correlation describes the relation between the cardiac preload and stroke volume (SV).[90] The assumption is that a fluid bolus increases cardiac preload and thereby SV. Starting from this theory, estimates of SV have been used to guide intravenous fluid therapy based on changes in SV. The SV goal-directed fluid therapy assumes that a patient is fluid responsive (hypovolemic) as long as a fluid bolus increases SV or related estimates reasonably. As such GDT possesses the ability to accommodate hypovolemic events and withhold fluid therapy when the desired change in SV is achieved. The Frank-Starling correlation is, however, influenced by numerous variables such as vasoactive drugs, sympathetic or para-sympathetic tone, and patient characteristics.[83]

1.4.1 Pre-, intra-, or post-operative fluid administration

Intravenous fluid therapy is given before, during, and after surgery. An adjunct in the urgent setting is that fluid administration is offered by several providers: the pre-hospital care team; the emergency care unit; the anaesthetic team during surgery; and after surgery by the team at the postoperative care unit, the intensive care unit, or at the surgical ward, which challenges the continuity of a fluid replacement strategy and an overview of the overall fluid loss and administration.

Pre-operative fluid therapy

The aim of preoperative fluid administration before emergency gastrointestinal surgery is to correct hypovolaemia as well as dehydration and bring plasma constitution close to normal. Typically, one to two litres of normal saline are given based on the patient's history and physiological status. The speed of the infusion depends on signs of hypovolemia. Most often, a slow infusion is commenced upon arrival to the emergency department.

Only one randomised trial has studied a perioperative fluid algorithm including the preoperative phase in high-risk patients undergoing abdominal surgery which included emergency procedures.[91] The study was, however, interrupted due to a slow inclusion rate after one year. The low number of included patients

prohibited analysis of the primary outcome. Studies addressing preoperative fluid administration before planned surgical procedures have found that preoperative administration of carbohydrate-containing fluids reduces the risk of nausea and vomiting, enhances well-being, and increases insulin sensitivity after surgery.[92–94] Overall, the effect of preoperative fluid optimisation in patients undergoing emergency abdominal surgery is unknown, but may yield a potential comparable with findings within planned procedures.

Intra-operative fluid therapy

The intraoperative period is included in most trials addressing perioperative fluid optimisation during abdominal surgery. Yet, only a few existing trials included patients with a need for emergency abdominal surgery: one pilot study,[40] two early-terminated studies,[41,91] and one study in which 3% (25) of 734 patients were emergency cases.[95] The studies provide inconsequential evidence of what fluid strategy to aim for in the emergency setting. Within planned abdominal surgery, goal-directed fluid strategies and zero-balance strategies have both been shown to reduce postoperative complications and length of hospital stay following abdominal surgery.[21,28,29,32,35,96]

Post-operative fluid therapy

No trials exist that study fluid optimisation following emergency gastrointestinal surgery. Following elective abdominal surgery, one study found an additional postoperative fluid volume administration to increase the time to gastric emptying and LOS.[27] Yet, another study found no difference in LOS when comparing a postoperative restrictive fluid regimen with a liberal regimen.[86] Conversely, one study was stopped prematurely due to an increased risk of postoperative complications and LOS in the restrictive fluid group.[97] All three studies included a small number of patients (between 20 and 62). Further, the restrictive and liberal regimens varied markedly, which may partly explain the varying results. In trials studying postoperative GDT optimisation, one study found a reduced risk of postoperative complications and LOS in the GDT group,[98] while another study found no significant difference in the risk of postoperative complications and death.[99]

Taken together, limited evidence is available regarding pre-, intra-, or post-operative fluid optimisation during emergency abdominal surgery. Moreover, the intra- and immediate postoperative fluid administration seems to be more strongly associated with postoperative complications than pre-operative fluid administration in studies of planned surgical procedures.

2 Methods

2.1 Methodological considerations

2.1.1 Study design

Retrospective studies provide valuable information on background data in a population but are predominantly descriptive. Comparison of study groups in a retrospective observational study is challenged by the risk of known and unknown confounding which omits deductions about causality.[100] Firm consideration about how to accommodate confounder correction is important. The selection of the study group may reduce some known confounders if the inclusion and exclusion criteria are carefully chosen. Analytical adjustment is another way to reduce the risk of confounders; however, the analytical adjustment depends on knowledge about confounders and the size of the study population. Importantly, the data extraction is limited to the available data and might restrain the research question.[101,102] The strength of retrospective data is that patient- and observer-related biases are minimised.[103,104] Moreover, retrospective studies allow the address of scientific questions in areas where randomised clinical trials are difficult to complete or may be unethical to perform.

A prospective randomised set-up addresses several of the limitations mentioned above when investigating the relation between an exposure and an outcome. When well conducted, the randomised set-up divides the cohort into comparable study groups and eliminates the risk of confounders. Further, the prospective collection of study-specific data ensures uniform registration of study-related variables in both groups. As such, a randomised clinical trial possesses the ability to demonstrate a causal relation between an exposure and an outcome. However, careful consideration about bias and confounding is still needed. In a non-blinded set-up, standardisation of the overall treatment alongside the intervention reduces potential confounders.

2.1.2 The setting of the studies

The retrospective cohort studies included patients from three of four hospitals in Zealand Region in Denmark with emergency uptake from approximately 800,000 residents. One hospital was excluded due to administrative challenges at the time and the patients in need of emergency surgery were redirected to the other hospitals in the region. The Danish Clinical Register of Emergency Surgery for peptic ulcer reported zero procedures at the excluded hospital during the study period,[53] and the number of gastrointestinal emergency surgical procedures was assumed to be very low, although unknown, at the excluded hospital. In all, the cohort is a thorough representation of the population in Region Zealand.

The prospective study was a randomised multicentre trial conducted at five hospitals in the eastern half of Denmark. Odense University Hospital and Svendborg Hospital are responsible for the general emergency uptake of approximately 495,000 inhabitants, Slagelse and Holbæk Hospitals of approximately 521,000 inhabitants, and Herlev Hospital of approximately 457,000 inhabitants, all together constituting a comprehensive representation of one-fourth of the Danish population.

2.1.3 The study population

Increased urgency of surgery seems associated with a rise in mortality.[48,105–107] To accommodate this consideration, sub-classifications such as immediate (minutes), urgent (hours), or expedient (days) need for surgery are used by the National Confidential Enquiry into Outcome and Death in England.[5,108,109] In comparison, the Danish Clinical Register of Emergency Surgery for gastric bleeding or perforation recommends a surgical/ endoscopic intervention within 3 hours of admission if the patient fails to respond to initial fluid resuscitation.[110] In alignment with this, we defined emergency surgery as the need for surgery without planned delay from the surgeon's decision for surgery.

Laparoscopic procedures have gradually been implemented in the urgent setting during the last few decades.[54,111,112] As such, we embedded both laparotomy and laparoscopic procedures in our study populations.

Based on National database enquiry, we chose to focus on the frail cohort of patients undergoing emergency surgery for gastrointestinal obstruction or perforation, which has a similar 30-day mortality risk. Patients with gastrointestinal bleeding have a noticeably lower 30-day mortality risk and were excluded from our study cohorts.

2.1.4 Preoperative assessment of patients

Several preoperative assessment tools exist to address the overall preoperative patient characteristics and estimate the postoperative risk of adverse events (e.g. the Charlson Comorbidity Index).[113] However, the majority of these tools are developed for patients undergoing planned surgical procedures.[114] We used ASA classification and the sepsis-2 score. For the GAS-ART trial we used the APACHE-II score, which, however, includes the initial postoperative period. Additional preoperative screening of patients was based on ungraded registration of co-morbidity.

2.1.5 Postoperative complications, classification

Classification of postoperative complications varies widely between studies, which hampers a comparison of study results. Postoperative complications may be graded according to the affected organ system (Postoperative Morbidity Survey),[115] the severity of a complication (Clavien-Dindo classification),[116] or an overall status of severity (The Comprehensive Complication Index).[117] Either approach has strengths and weaknesses. Importantly, uniform classification of complications challenges the fundamental principles of hypothesis testing. The relation between an exposure and an outcome may focus on a study-specific complication or a group of related complications developing in continuums. Further, retrospective registration of complications may differ from prospective registration of complications, since the requirement of diagnostic actions is obsolete in the former.

We chose to define the postoperative complications according to Table 1. The definitions of the complications are similar to the definitions used in previous prospective trials that study the relation between a perioperative fluid therapy and postoperative complications.[21,118] In general, a complication was accepted if it warranted medical or surgical treatment. In the prospective trial, additional requests for diagnostic tests were required. The strict definitions decrease subjective interpretation of events.

Additionally, we chose to grade the retrospectively registered complications according to the Clavien-Dindo classification (CDC), which allowed us to divide the complications according to their severity in minor (CDC<3) or major (CDC≥3) complications in papers I and III.[116] The CDC was originally developed for elective surgical patients. In 2014 Mentula and colleagues suggested the use of CDC following emergency surgery, and it has been gradually implemented in that area.[46,119,120]

2.2 Statistical considerations

The fundamental of hypothesis testing in medical sciences is the null hypothesis, assuming no difference of intervention between compared groups.[121] The significance level (α) is the maximal accepted probability of making a type I error or incorrectly rejecting the null hypothesis and is usually assigned a value of 0.05. In a series of hypothesis testing, the risk of making a type I error (the study-wise error rate) is given by $1 – (1 – \alpha)^n$, where n is the number of independent tests.[122] It follows that the study-wise error rate increases by the number of tests performed. The Bonferroni adjustment ensures that the study-wise error rate remains at 0.05 when performing multiple independent tests and is given by $1 – (1 – \alpha)^{1/n}$ or approximated by α/n.[123] In other words, when comparing *similar* groups with multiple tests, the Bonferroni adjustment ensures that the risk of type I errors does not increase. However, a true difference between the groups may

exist. The inevitable consequence of Bonferroni adjustment is an increased risk of a type II error (β) or the acceptance of an incorrect null hypothesis.[124]

Correction for multiple testing is debatable as the study structure, the outcome, and the hypothesis tested need to be considered. Prospective randomized trials seek causal relations with potential external applicability of a study intervention. As such, type I errors might at best be unjustified although they are potentially detrimental.[125] Conversely, rejecting a true effect of an intervention may set back scientific progress. Thus, one needs to consider whether the interpretation of one test reasonably depends on the number of other tests performed. Retrospective cohort trials are generally hypothesis generating and adjustment of the significance level is aimed at reducing random findings but has been argued to undermine the basics of hypothesis-testing.[121,123] Further, which tests to adjust for is debatable. Adjustment of the significance level needs to be considered when performing multiple tests in a study, e.g. subgroup analysis, sequential testing, or in case of explorative testing of significant associations.[122] However, interpreting scientific results essentially relies on critical assessment of the study set-up, the analysis performed, and considerations about a plausible biological relation.

2.3 Methods used in the papers

The observational retrospective multicentre studies (papers I and III) collected data on patients admitted between 1 July 2014 and 31 July 2015 at Holbæk, Slagelse, and Køge hospitals in Region Zealand. The prospective multicentre trial (paper II) was conducted as a randomised clinical drug trial (protocol given in paper IV). Patients were enrolled at Svendborg, Odense, Slagelse, Holbæk, and Herlev hospitals between August 2015 and August 2018.

Inclusion and exclusion criteria were similar between the observational and prospective studies. We included adult (≥18 years) patients with radiologically verified gastrointestinal obstruction or perforation. We excluded patients who had had intraabdominal surgery in a 30-day period prior to the index procedure, patients in regular dialysis, pregnant at the time of surgery, or with a traumatic or iatrogenic perforation.

The difference between the prospective and retrospective cohorts is related to the study design. In the retrospective trials only, Danish residents were included to ensure complete follow-up.[127] In the prospective trial, inclusion was only possible when an anaesthetist capable of conduction the intervention was present. Further, only patients given informed consent were included and palliative procedures (ASA class 5–6) were excluded.

2.3.1 Exposure variables

The exposure variable in papers I and II was perioperative fluid balance estimated as the difference between fluid administration (intravenous and per oral fluid administration) and fluid loss (physiological and pathological). We included all registered fluid variables and estimated the perspiration to be 0.5 mL kg^{-1} $hour^{-1}$. In paper I the perioperative fluid balance was calculated from induction of anaesthesia and to discharge from the postoperative care unit or intensive care unit for a maximum of 24 hours. In paper II the perioperative fluid balance was calculated from induction of anaesthesia and to the end of the postoperative day 1. The cohort was divided at a perioperative fluid balance of 2.5 L in paper I. In paper II we used the results from paper I as indices of an optimal fluid balance during emergency gastrointestinal surgery and divided the cohort at 0.0 L and 2.0 L. The exposure variable in paper III was 16 predefined postoperative complications. In paper IV we present two different methods of perioperative fluid administration as exposure (GDT and postoperative zero-balance versus a standardised fluid regimen).

2.3.2 The outcome

Five outcomes were analysed in paper I (overall, cardiopulmonary, renal, infectious, and wound-related complications) and one outcome in paper II (cardiopulmonary complications). Death was the outcome in paper III. We introduced a composite outcome in paper IV of major complications and death.

2.3.3 Study conduction and data collection

We collected data retrospectively in papers I and III between 15 June 2017 and 31 March 2018. The electronic booking system of surgical procedures was manually screened, and all potentially eligible patients registered. Each patient record was assessed to evaluate patients eligible for inclusion. Prior to data extraction, each research member of the research team was instructed in the use of the case report form, the definitions of sepsis-2 criteria, the Clavien-Dindo classification, the ASA classification, and the definition of complications presented in Table 1.

Each patient record was assessed twice by two independent researchers and the registration of complications were collected in two separate case report forms identified by the individual civil registration numbers of the patient. Data on perioperative fluid administration were collected by two researchers to ensure comprehensive data collection from the software system. The interconnected civil registration system provided complete data on mortality.[127] Database entry of all case report forms ensured double registration. The project leader assessed and corrected the database for irregularities according to the protocolled definitions and study-specific 'standard operating procedures'. Interpretative challenges were solved in dialogue with the senior consultant responsible for the trial.

The overall rationale and methods used in the GAS-ART trial are presented in paper IV. Five hospitals were included as study sites in the GAS-ART trial based on dedicated and motivated trial physicians from the surgical and anaesthetic wards. The trial physicians were selected to lead and implement the study. Their thorough knowledge and understanding of the protocol were confirmed by the project leader. Further, introduction to the GDT equipment was ensured by the project leader and a product specialist. Formal teaching of physicians and nurses at the surgical ward, anaesthetic ward, PACU, and the ICU were conducted before and during the months after the initiation. The GAS-ART trial was initiated consecutively at the hospitals with two months apart. Weekly contact with the trial physicians and visits every second month at the project sites ensured continuously focus on the trial and handling of project matters. Project status meetings were arranged each year. Several local initiatives were arranged to maintain project commitment and enhance patient recruitment.

Data from the GAS-ART trial were used for the prospective cohort study (paper II). The data were collected in case rapport forms and the patient files. The trial adhered to the International Council for Harmonisation – Good Clinical Practice guidelines. An independent monitoring unit controlled the data collection and protocol adherence. Outcome was evaluated during admission by clinical evaluation of the patients. Follow-up on postoperative day 30 and 90 was ensured by phone. Finally, a blinded assessment of the postoperative complications was conducted and validated. Disagreements in outcome were settled by another blinded assessor.

2.3.4 Ethical considerations

Study approval for the observational studies was granted by the Danish Data Protection Agency and the Danish Patient Safety Authority. Patient consent was wavered by the Ethics Committee. Permission to initiate the GAS-ART trial was granted by the Danish National Committee on Health Research Ethics, the Danish Data Protection Agency, and the Danish Patient Safety Authority. Patient consent was warranted according to ethic and legislative requirement. Patients enrolled in the GAS-ART trial were not subject to any additional risk, since the use of arterial lines for blood pressure monitoring was usual practice in patients undergoing emergency surgery at the involved hospitals. However, Ringers solutions, Saline, and Albumin 5% were registered as drugs in the GAS-ART trial and Serious Adverse Reaction or Suspected Unexpected Serious Adverse Reaction were registered and reported to the Danish Patient Safety Authority (now the Danish Medicines Agency).

2.4 Statistics used in the papers

Continuous variables following a Gaussian distribution were presented by parametric statistics; otherwise, non-parametric statistics were used. Nominal data were given by number and percent. The primary outcome was presented with a 95% confidence interval and 5% level of significance. Bonferroni adjustment was used in paper I based on 5 outcome markers and in paper III, based on 16 exposure variables.[122,125] Data were analysed using R version 3.5.0 GUI 1.70 El Capitan ©R, 2016 and RStudio version 1.1.453.

We analysed the primary outcome by an adjusted regression model in papers I, II, and III. In paper I adjustment of the logistic regression was based on a priori knowledge of variables known to influence the exposure and outcome: sex, age,[128] ASA class (grouped in ASA I-II or III-V),[43] use of epidural analgesia (yes or no),[129] use of vasopressors (yes or no),[6] the type of surgery (bowel resection, palliative surgery, or other procedure),[48] the intraabdominal pathology (gastrointestinal obstruction or perforation), [107] and the hospital. Sensitivity analysis was planned excluding patients with a preoperative sepsis-2 score of 3–4 or

patients admitted directly to the intensive care unit after surgery. In paper II a weighted propensity score was used to adjust the logistic regression analysis and the middle group served as reference. In paper III Cox regression with delayed entry was adjusted by variables significantly ($p<0.05$) associated with the outcome in a univariate analysis. Sub-group analysis was planned for patients with gastrointestinal obstruction or perforation. In papers I and II we used smoothing splines with four degrees of freedom to explore the association between the predicted risk of complications and fluid balance on a continuous scale. Odds ratio (OR) with a 95% confidence interval (CI) presented the results in papers I and II and Hazard ratio (HR) with a 95% CI in paper III. Based on the Bonferroni adjustment a $p<0.01$ was considered significant in paper I, a $p<0.05$ in paper II, and a $p<0.003$ in paper III.

3 Summary of results

3.1 Observational study (paper I)

A total of 342 patients were included (Figure 1). The cohort was divided into a conservative and a liberal fluid group at a perioperative fluid balance of 2.5L. Fewer patients in the conservative group had active cancer or renal disease, and gastrointestinal perforation. Further, fewer patients had a sepsis-2 score of 3–4 and an ASA score between 3 and 5. Additionally, the duration of surgery was shorter, and the patients were less frequently admitted to the intensive care unit after surgery.

The median [IQR] perioperative fluid balance was 1.6 L [1.0, 2.0] (3.3 mL kg^{-1} $hour^{-1}$) in the conservative group compared with 3.6 L [3.0, 5.3] (4.7 mL kg^{-1} $hour^{-1}$) in the liberal group (Table 2). More hypotensive episodes were registered in the liberal group during and after surgery, and more patients received postoperative vasopressor treatment in the liberal group. The overall risk of complications was 66% (Table 3). A perioperative positive fluid balance above 2.5 L was significantly associated with an increased risk of overall complications, (OR (95% CI), 2.6 (1.5–4.4), $p<0.001$) and the sub-group of cardiopulmonary complications, OR 3.2 (1.9–5.7), $p<0.001$. The sensitivity analysis did not change the result.

A U-shaped association between perioperative fluid balance and the predicted risk of overall (Figure 2), cardiopulmonary (Figure 3a), or renal complications (Figure 4a) was found but was, however, only a good fit for the two latter. A perioperative fluid balance of approximately 0–2 L was associated with the lowest predicted risk of cardiopulmonary complications (Figure 3a). However, a perioperative fluid balance of 1.5–3.5 L was associated with a lowest predicted risk of renal complications (Figure 4a). The predicted risk of infectious complications increased significantly as the fluid balance increased (Figure 5a). No relation was found between the wound-related complications and the fluid balance on a continuous scale (Figure 6a).

3.2 Prospective cohort study (paper II)

A total of 303 patients were included in the analysis and divided into a Low-FB (fluid balance) (n=44), Moderate-FB (n=108), or High-FB (n=151) group at a perioperative fluid balance of 0.0 L and 2.0 L (Table 4). Patients in the Low-FB group were younger and more frequently had a liver disease or active cancer than the two other groups. The intraabdominal pathology was dominated by small bowel obstruction. Patients in the High-FB group had a higher incidence of heart disease, a higher sepsis-2 score, and more often gastrointestinal perforation. Hence, more patients in the High-FB group had a sepsis-2 score of 3–4 and were admitted to the intensive care unit directly after surgery. More patients received vasopressor treatment after surgery in the High-FB group.

In the Low-FB group, the median [IQR] perioperative fluid balance was –0.9 L [–1.4, –0.6], compared with 0.9 L [0.5, 1.3] in the Moderate-FB group, and 3.8 L [2.7, 5.3] in the High-FB group (Table 5). Cardiopulmonary complications appeared in 16.2% (49) of the patients. Cardiopulmonary complications were significantly associated with the High-FB group, OR 3.4 (1.5–7.6), p=0.002 (Table 5). The Low-FB group was not significantly associated with the risk of cardiopulmonary complications. The predicted risk of cardiopulmonary complications was at a minimum at a fluid balance of approximately –1 L to 1 L based on the spline model (Figure 3b). We found no significant association between the secondary outcome and the fluid groups. On a continuous scale of the fluid balance, renal complications increased significantly with an increase of the fluid balance (Figure 4b).

3.3 Observational study (paper III)

A total of 349 patients were included (Figure 1). During the 90 days of follow-up 832 complications were registered in 281 (81%) patients and the risk of death was 26% (91 patients). The patients with complications more often had renal comorbidity, a higher ASA class, and gastrointestinal perforation. The patients who died were older, had more cardiac or renal comorbidity, had active cancer, and presented with a higher sepsis-2 score or ASA class. Additionally, the patients who died more often had gastrointestinal perforation.

Between postoperative day 0–7, a total of 525 (63%) complications appeared. The most frequent complication was prolonged paralysis present in 145 (42%) of the patients (Table 6). The risk of death, according to the individual complications, ranged from 21% for patients with prolonged paralysis and up to 57% for patients with renal impairment. Ten complications were significantly associated with death in the crude analysis with hazard rates ranging from 2.4 (1.5−3.9), p=0.0006 for re-operations and up to 6.8 (3.7–12.4), p <0.0001 for renal impairment (Table 7). Seven significant associations were found in the adjusted analysis of ten performed analyses, of which the strongest association was observed for atrial fibrillation, HR 3.3 (2.1–5.2), p<0.0001 and deep wound complications, HR 3.2 (1.7–5.8), p=0.0001. Atrial fibrillation was the only complication significantly associated with death in both the subgroups of patients with gastrointestinal obstruction or perforation (Table 8).

Table 1 – Definition of postoperative complications

Complication	Definition in the retrospective studies	Definition in the prospective study
Superficial wound rupture	Conservative or surgical treatment	
Superficial wound haematoma*	Not registered	Observed by a physician
Superficial wound infection	Wound rupture, a need for removal of infected tissue, or medical treatment	
Deep wound infection and fascial defect	A need for surgical cleavage or removal of infected tissue with fascial defect	
Fascial rupture	Spontaneous fascial rupture	
Anastomosis leakage	Symptomatic and requiring treatment	
Separation of stoma	Cutaneous and subcutaneous defect	
Re-perforation	A need for re-laparotomy	
Peritonitis	Debut postoperatively	Debut intra- or postoperatively
Intraabdominal abscess	Suspected radiologically with a need for medical or surgical treatment	
Postoperative obstruction of intestine	A need for re-laparotomy	
Prolonged paralysis of intestine	≥4 days without defecation [126]	≥7 days without defecation
Gastrointestinal bleeding	A need for surgical or endoscopic treatment	
Re-operation	Any unplanned re-operation	
Packed blood products	Transfusion with packed blood, thrombocytes, or plasma	Not registered
Septicaemia	Not registered	Worsening postoperatively, debut intraoperatively or postoperatively, graded according to sepsis-2 definitions
Pneumonia	Diagnosed by the treating physician and medical treatment initiated	Radiological documentation, ≥one clinical sign (fever, leucocytosis, coughing or crepitation), and treatment initiated
Urinary tract infection	Diagnosed by the treating physician and medical treatment initiated	Symptomatic, documented bacteriuria, and treatment initiated
Atrial arrhythmia	Verified by electrocardiogram and a need for treatment	
Ventricular arrhythmia	Verified by electrocardiogram and a need for treatment	
Acute myocardial infarction	ECG-pathology and treatment initiated	ECG-pathology and elevated cardiac-enzymes
Cardiac arrest	Diagnosed by a physician with or without successfully resuscitation	
Exudation to the pleural cavity	Verified by radiology	
Pulmonary congestion	With a need for medical treatment	Suspected clinically with bilateral crepitation and positive effect of diuretic treatment
Pulmonary oedema	Radiographic suspicion and a need for intensive care	
CPAP	A need for non-invasive ventilation or continuous positive airway pressure (CPAP) after the day of extubation	Not registered
Failure to wean	Intubation continued for more than 48 hours after surgery	Not registered
Re-intubation	Re-intubation of any cause	Not registered
Mechanical respiratory support	Not registered	A need for intubation or continuous non-invasive ventilation
Acute respiratory distress syndrome	According to the Berlin definition	
Deep venous thrombosis	Verified by radiology	
Pulmonary embolism	Verified by scintigraphy or CT-scan	
Disseminated intravascular coagulopathy	Diagnosed by the treating physician	
Stroke or cerebral haemorrhage	Relevant radiology or diagnosed by neurologist	Neurological symptoms and relevant radiology or diagnosed by neurologist
Delirium / psychosis	Not registered	Deficiency in orientation, level of consciousness, cognition and/or psychosis
Renal failure	A need for dialysis	
Other complication	With a need for medical or surgical intervention	

* Bold caption indicates dissimilar definitions

Figure 1. Overall trial profile for the cohort studies (papers I and III)

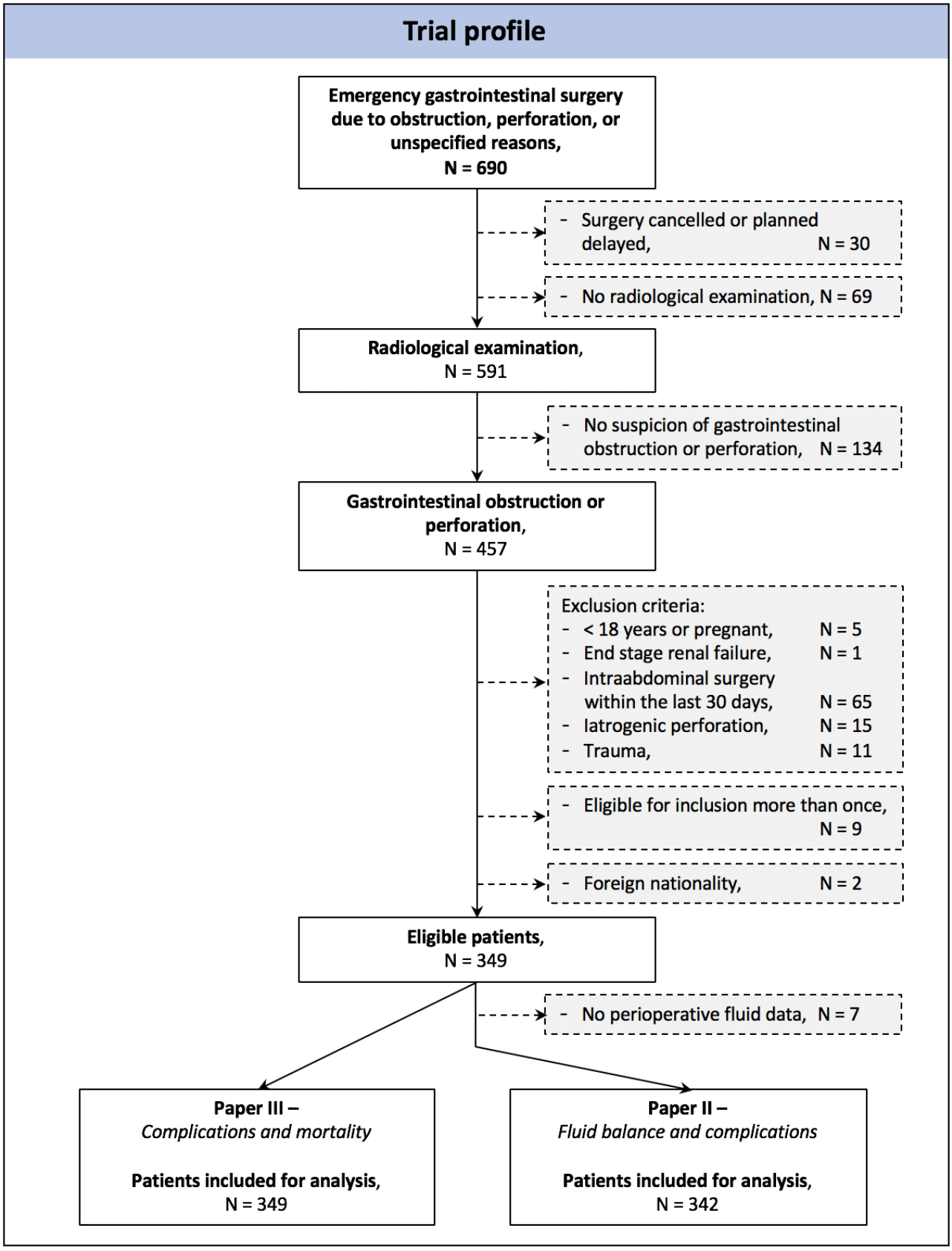


Table 2. Peri-operative data from patients undergoing emergency gastrointestinal surgery (paper I).

	Conservative group (peri-operative balance ≤2.5 L), n = 179	Liberal group (peri-operative balance >2.5 L), n = 163
Pre-operative data		
Pre-operative Sepsis-2 score		
0-2, No (%)	162 (91.5)	126 (77.8)
3-4, No (%)	15 (8.5)	36 (22.2)
Peri-operative fluid data#		
Total iv fluid administration, mL, median [IQR]	2610 [2160, 3310]	6000 [4290, 8930]
Total loss, mL, median [IQR]	920 [480, 2000]	1900 [960, 3350]
Fluid balance, mL, median [IQR]	1580 [1000, 2040]	3620 [3020, 5340]

#) Including intra-operative data and data up to 24 hours postoperative.

Table 3. Logistic regression analysis on the association between the peri-operative fluid balance and post-operative complications (paper I)

Complication	Conservative group, N = 179 No. of patients (%)	Liberal group, N = 163 No. of patients (%)	Crude OR (95% CI) *	Crude p	Adjusted analysis¤ OR (95% CI) *	Adjusted analysis¤ p
Primary outcome						
Overall complications	98 (58.0)	127 (73.4)	2.9 (1.8-4.7)	<0.001	2.6 (1.5-4.4)	<0.001
Subgroups of outcome						
Wound-related	39 (23.1)	48 (27.7)	1.5 (0.9-2.5)	0.105	1.6 (0.9-2.7)	0.123
Superficial wound ruptur	18	25				
Rupture of the fascia	20	20				
Leakage of anastomosis	1	3				
Cardiopulmonary	45 (26.6)	89 (51.4)	3.6 (2.3-5.7)	<0.001	3.2 (1.9-5.7)	<0.001
Arrhythmia	14	28				
AMI#	2	2				
Cardiac arrest	2	0				
Pleural effusion	9	17				
Pulmonary congestion	5	14				
Pulmonary oedema	2	2				
Respiratory failure	11	26				
Renal	7 (4.1)	15 (8.7)	2.5 (1.0-6.7)	0.053	-	-
Need for dialysis	2	3				
Other renal§	5	12				
Infectious	73 (43.2)	90 (52.0)	1.8 (1.2-2.8)	0.008	1.6 (1.0-2.5)	0.071
Wound infection	14	12				
Pneumonia	35	65				
Urinary tract infection	18	11				
Other infections	6	2				

¤) Clinical risk factors adjusted for in the model: Sex, age in the potency, ASA class (dichotomized at ASA class 3), use of epidural analgesia (yes or no), use of vasopressors (yes or no), the type of surgery (bowel resection, palliative surgery or other procedures), gastrointestinal obstruction or perforation, and the Hospital (Holbæk, Slagelse, or Køge). *) OR: Odds ratio, 95% CI: 95% confidence interval. #) Acute myocardial infarction §) Hydronephrosis with nephrostomy catheter or treatment stalled due to renal failure. A p-value < 0.01 was considered significant.

Table 4. Peri-operative data from patients undergoing emergency gastrointestinal surgery (paper II).

	Low-FB§ group (fluid balance <0.0L) n = 44	Moderate-FB group (fluid balance 0.0-2.0L) n = 108	High-FB group (fluid balance >2.0L) n = 151
Pre-operative data			
Pre-operative Sepsis-2 score			
0-2, No (%)	43 (97.7)	107 (99.1)	135 (89.4)
3-4, No (%)	1 (2.3)	1 (0.9)	16 (10.6)
Randomisation, GDT-group, No (%)	26 (59.1)	62 (57.4)	62 (41.1)
Peri-operative fluid data#			
Total fluid administration, mL, median [IQR]	4380 [3250, 5540]	4880 [3500, 6230]	7820 [6120, 9800]
Total fluid loss, mL, median [IQR]	5700 [4110, 7690]	4000 [2480, 5170]	3640 [2620, 5080]
Fluid balance, mL, median [IQR]	-870 [-1440, -550]	930 [540, 1330]	3760 [2730, 5290]

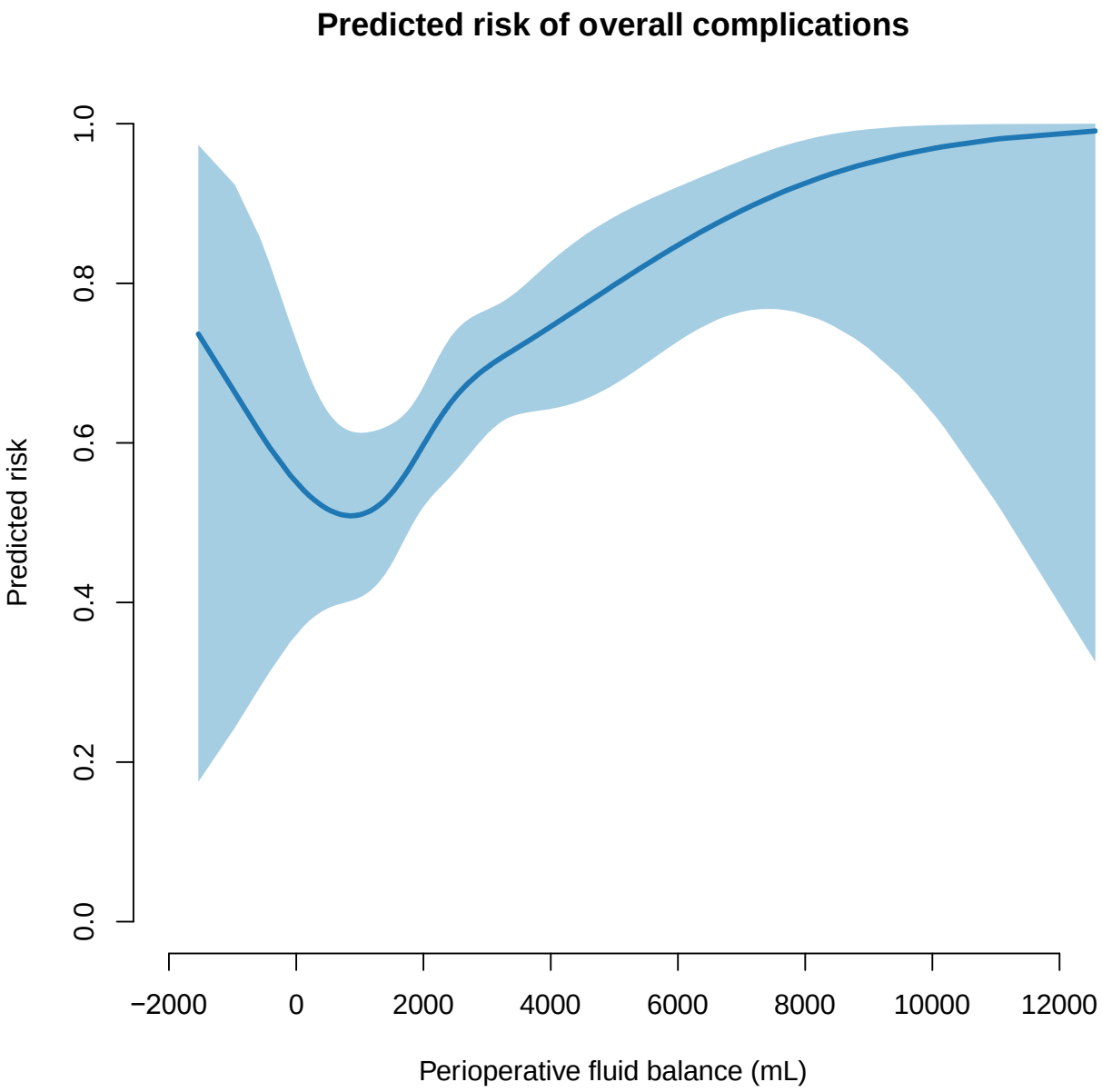
§ Fluid Balance. #) Including intra-operative data and data up to 48 hours postoperative.

Table 5. Logistic regression analysis on the association between the peri-operative fluid group and post-operative complications (paper II).

	Low-FB§ group (fluid balance <0.0L)		Moderate-FB group (fluid balance 0.0-2.0L)	High-FB group (fluid balance >2.0L)	
	OR* (95% CI)	p value		OR (95% CI)	p value
	Crude analysis				
Primary outcome					
Cardiopulmonary complications	1.1 (0.3-3.6)	0.880	Ref#	3.4 (1.6-7.9)	0.002
Secondary outcome					
Renal complications	1.1 (0.3-3.3)	0.830	Ref	1.7 (0.8-3.9)	0.147
Infectious complications	0.8 (0.3-1.8)	0.598	Ref	1.2 (0.7-2.0)	0.605
Wound-related complications	0.7 (0.3-1.9)	0.552	Ref	0.6 (0.3-1.2)	0.149
	Adjustedθ analysis				
Primary outcome					
Cardiopulmonary complications	1.7 (0.5-6.1)	0.44	Ref	3.4 (1.5-7.6)	0.002
Secondary outcome					
Renal complications	0.9 (0.5-1.7)	0.86	Ref	1.7 (0.8-3.6)	0.20
Infectious complications	0.8 (0.3-1.8)	0.57	Ref	1.0 (0.6-1.9)	0.90
Wound-related complications	0.8 (0.3-2.3)	0.73	Ref	0.6 (0.3-1.3)	0.19

§ Fluid balance. * Odds ratio (95% confidence interval). # The Moderate-FB group serves as reference in bi-variate analysis. θ Adjusted by a weighted propensity score. A p-value<0.05 was considered significant.

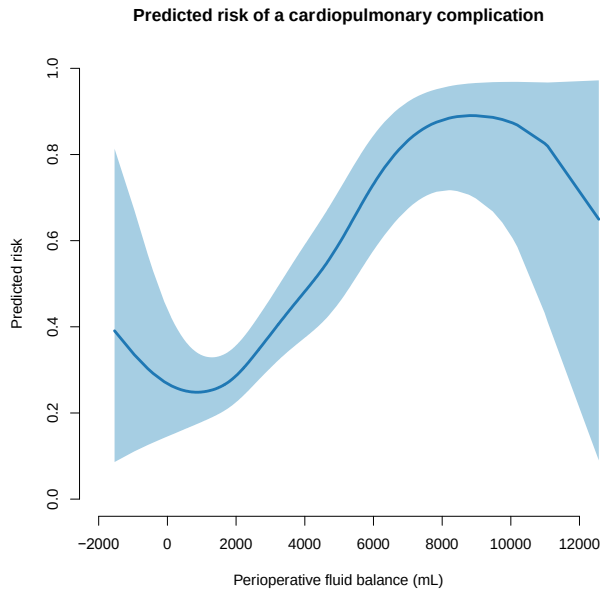
Figure 2. Predicted risk of overall complications associated with the perioperative fluid balance following emergency gastrointestinal surgery (paper I).



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect is p<0.001 and the non-parametric effect is p=0.572. A p-value <0.01 is considered significant.

Figure 3. The predicted risk of a cardiopulmonary complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery (papers I and II).

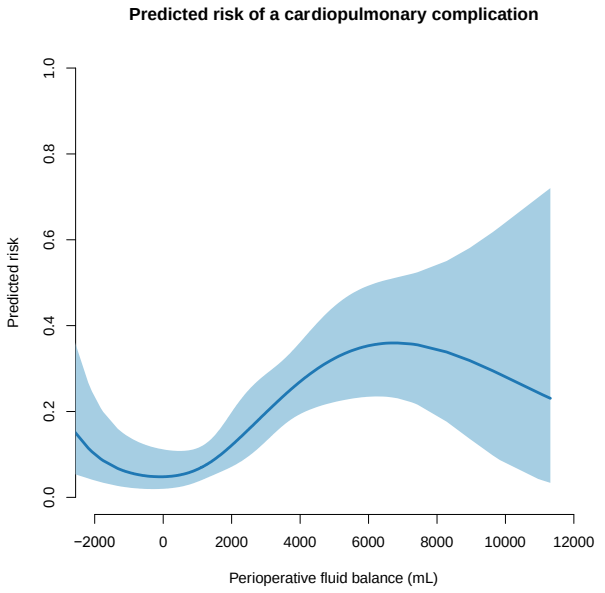
a. Data from the retrospective cohort, paper I



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalized additive model with smoothing splines and four degrees of freedom. The parametric effect is p<0.001 and the non-parametric effect is p=0.015. A p-value <0.01 was considered significant.

Cardiopulmonary complications included atrial or ventricular arrhythmia, acute myocardial infarction, cardiac arrest, pleural exudation, pulmonary congestion, or respiratory failure (re-intubation, failure to wean, or a need for continuous positive airway pressure or non-invasive ventilation).

b. Data from the prospective cohort, paper II

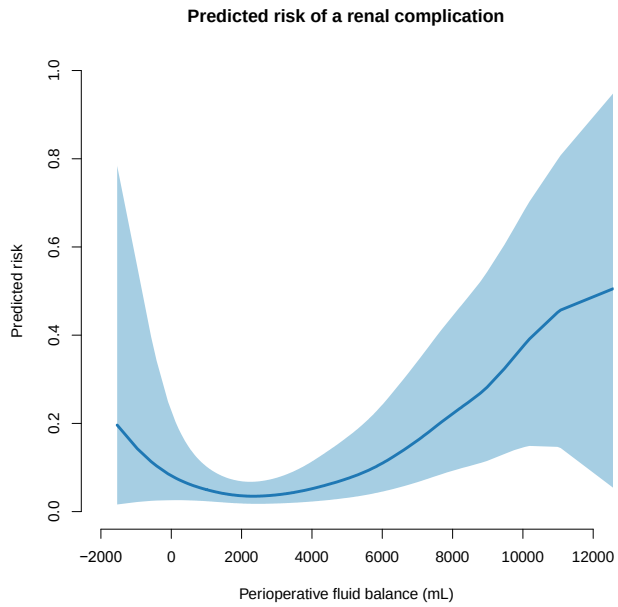


The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect is p<0.001 and the non-parametric effect is p=0.008. A p-value <0.05 was considered significant.

Cardiopulmonary complications included atrial or ventricular arrhythmia, acute myocardial infarction, cardiac arrest, pleural exudation, pulmonary congestion, or respiratory failure with a need for mechanical ventilation.

Figure 4. The predicted risk of a renal complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery (paper I and II).

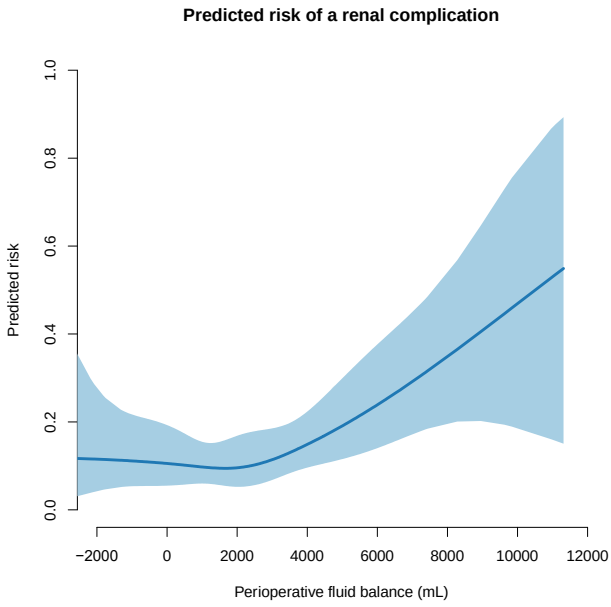
a. Data from the retrospective cohort, paper I



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalized additive model with smoothing splines and four degrees of freedom. The parametric effect is p<0.001 and the non-parametric effect is p=0.080. A p-value <0.01 was considered significant.

Renal complications included a need for dialysis, hydronephrosis with a need for nephrostomy catheter, or renal failure not treated.

b. Data from the prospective cohort, paper II

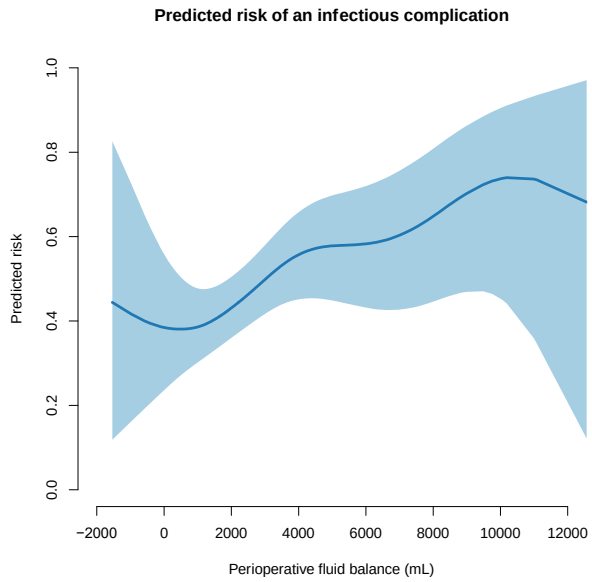


The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect is p=0.004 and the non-parametric effect is p=0.334. A p-value <0.05 was considered significant.

Renal complications included a need for dialysis, hydronephrosis with a need for nephrostomy catheter, or acute kidney injury defined as an increase of s-Creatinine by >26.5 mmol L^{-1} within 48 hours post-surgical.

Figure 5. The predicted risk of an infectious complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery (papers I and II).

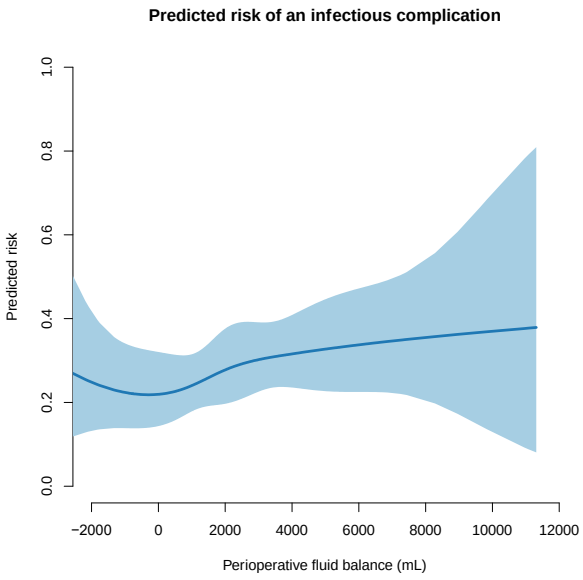
a. Data from the retrospective cohort, paper I



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect p=0.004. The non-parametric effect p=0.358. A p-value <0.01 was considered significant.

Infectious complications included superficial or deep wound infection, urinary tract infection, pneumonia, and other infections (cutaneous infections, e.g. erysipelas)

b. Data from the prospective cohort, paper II

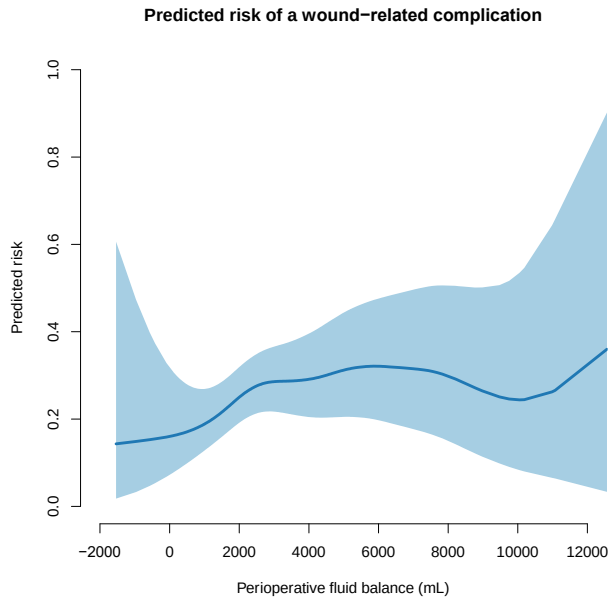


The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect is p=0.162 and the non-parametric effect is p=0.680. A p-value <0.05 was considered significant.

Infectious complications included superficial or deep wound infection, urinary tract infection, pneumonia, and intraabdominal abscess formation.

Figure 6. The predicted risk of a wound-related complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery (papers I and II).

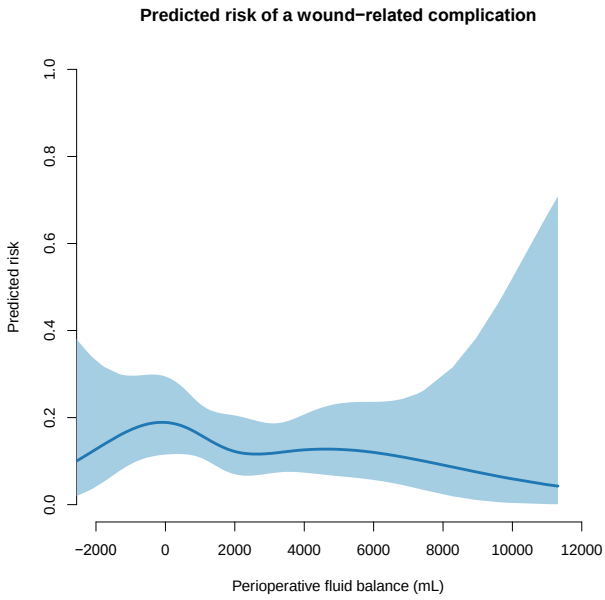
a. Data from the retrospective cohort, paper I



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect p=0.182. The non-parametric effect p=0.187. A p-value <0.01 was considered significant.

Wound complications included superficial wound rupture, fascia rupture, and leakage of the anastomosis.

b. Data from the prospective cohort, paper II



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect is p=0.386 and the non-parametric effect is p=0.412. A p-value <0.05 was considered significant.

Wound complications included superficial wound rupture, superficial wound infection, deep wound infection, and fascia rupture.

Table 6. Risk of a complication according to the postoperative day (POD) following emergency surgery for gastrointestinal obstruction or perforation.

Complication	Events / missing dates	POD 0-1	POD 2-7	POD 8-14	POD 15-30	POD 31-90
		Patients with a complication, No (%)				
Superficial wound complication	81 / 5	5 (6.2)	20 (24.7)	22 (27.2)	22 (27.2)	7 (8.6)
Superficial wound rupture	43					
Superficial wound infection	38					
Deep wound complication	45 / 0	1 (2.2)	23 (51.1)	16 (35.6)	4 (8.9)	1 (2.2)
Deep wound infection	5					
Fascia dehiscence	40					
Peritonitis	24 / 0	0 (0.0)	8 (33.3)	8 (33.3)	7 (29.2)	1 (4.2)
Peritonitis	4					
Intraabdominal abscess	20					
Prolonged paralysis	145 / 0	-	145 (100.0)	-	-	-
Gastrointestinal bleeding	19 / 0	5 (26.3)	6 (31.6)	4 (21.1)	2 (10.5)	2 (10.5)
Packed blood-products	47 / 6	12 (25.5)	24 (51.1)	3 (6.4)	2 (4.3)	0 (0.0)
Pneumonia	110 / 6	21 (19.1)	48 (43.6)	21 (19.1)	8 (7.3)	6 (5.5)
Urinary tract infection	44 / 4	3 (6.8)	7 (15.9)	6 (13.6)	12 (27.3)	12 (27.3)
Atrial fibrillation	63 / 4	28 (43.8)	25 (39.1)	3 (4.7)	1 (1.6)	2 (3.2)
Pleural exudation	62 / 6	4 (6.5)	18 (29.0)	21 (33.9)	6 (9.7)	7 (11.3)
Pulmonary oedema	53 / 4	10 (18.9)	26 (49.1)	6 (11.3)	4 (7.5)	3 (5.7)
Pulmonary congestion	41					
Pulmonary oedema	12					
Respiratory failure	63 / 0	7 (11.1)	42 (66.7)	11 (17.5)	2 (3.2)	1 (1.6)
CPAP¤	24					
Failure to wean (>48h)	21					
Re-intubation	18					
Venous TEEΦ	6 / 0	0 (0,0)	1 (16.7)	2 (33.3)	0 (0.0)	3 (50.0)
Deep venous thrombosis	2					
Pulmonary embolus	4					
Arterial TEE	17 / 0	3 (17.6)	7 (41.2)	2 (11.8)	1 (5.9)	4 (23.5)
Acute myocardial infarction	9					
Stroke	4					
DIC*	3					
Arterial thrombosis	1					
Renal impairment	23 / 0	3 (13.0)	9 (39.1)	2 (8.7)	3 (13.0)	6 (26.1)
Renal failure	8					
Other renal	15					
Re-operation	79 / 0	4 (5.1)	37 (46.8)	25 (31.6)	6 (7.6)	7 (8.9)
Superficial wound rupture	9					
Deep wound rupture	37					
Anastomotic leakage	2					
Separation of stoma	1					
Re-perforation	6					
Peritonitis or abscess	2					
Post-operative obstruction	21					
Laparotomy pro haemostasis	1					
Death	91 / 0	19 (20.9)	9 (9.9)	14 (15.4)	15 (16.5)	34 (37.4)

¤ Continuous positive airway pressure. Φ Thrombo-embolic events. § Acute myocardial infarction. * Disseminated intravascular coagulation.

Table 7. Risk of a complication or all-cause mortality and their association following emergency gastrointestinal surgery (paper III).

	Risk of a complication	Death (modified FTR§)	Crude analysis		Adjusted analysisθ	
	n (%)	n (%)	HR (95% CI)#	p	HR (95% CI)	p
Superficial wound complication	81 (24)	20 (25)	1.7 (1.0-2.9)	0.0393	1.6 (0.9-2.7)	0.1204
Deep wound complication*	45 (13)	16 (36)	2.5 (1.4-4.4)	0.0015	3.2 (1.7-5.8)	0.0001
Peritonitis	24 (7)	9 (38)	2.6 (1.3-5.4)	0.0067	-	-
Prolonged paralysis	145 (43)	30 (21)	1.1 (0.7-1.7)	0.8060	1.3 (0.8-2.2)	0.2872
Gastrointestinal bleeding	19 (6)	7 (37)	2.8 (1.3-6.2)	0.0084	-	-
Packed blood-products	47 (14)	21 (45)	3.1 (1.9-5.2)	<0.0001	1.7 (1.0-2.9)	0.0643
Pneumonia	110 (32)	40 (36)	3.4 (2.2-5.3)	<0.0001	2.4 (1.5-3.8)	0.0003
Cystitis	44 (13)	11 (25)	2.0 (1.0-3.8)	0.0376	1.7 (0.8-3.4)	0.1494
Atrial fibrillation	63 (19)	33 (52)	4.4 (2.8-6.8)	<0.0001	3.3 (2.1-5.2)	<0.0001
Pleural exudation	62 (18)	26 (42)	3.9 (2.4-6.4)	<0.0001	2.3 (1.4-4.0)	0.0019
Pulmonary oedema	53 (16)	25 (47)	4.0 (2.5-6.4)	<0.0001	2.3 (1.4-3.8)	0.0011
Respiratory failure	63 (18)	29 (43)	3.1 (2.0-4.8)	<0.0001	2.9 (1.6-5.1)	0.0003
Venous TEEΦ	6 (2)	2 (33)	2.6 (0.6-10.6)	0.1840	-	-
Arterial TEEΦ	17 (5)	8 (47)	4.8 (2.3-9.9)	<0.0001	-	-
Renal impairment	23 (7)	13 (57)	6.8 (3.7-12.4)	<0.0001	-	-
Re-operation	79 (23)	25 (32)	2.4 (1.5-3.9)	0.0006	2.7 (1.6-4.5)	0.0001

§ Failure-to-rescue. # Hazard Ratio (95% Confidence interval). θ Variables adjusted for in the multivariable analysis: hospital (Holbæk, Slagelse, and Køge), age, ASA class (categorised at 1-2 or 3-5), pre-operative sepsis-2 score (categorised at 0–2 or 3–4), cardiac co-morbidity (yes or no), hypertension (yes or no), renal co-morbidity (yes or no), active cancer (yes or no), the diagnosis (bowel obstruction or perforation), and the type of surgery (bowel resection and stoma formation or other procedures). *Analysed for laparotomies only, excluding 22 laparoscopic procedures. Φ Thrombo-embolic events. A p-value <0.003 was considered significant.

Table 8. The association between complications and 90-days mortality stratified on gastrointestinal obstruction or perforation (paper III).

	Gastrointestinal obstruction				Gastrointestinal perforation			
	Risk of a complication, n (%)	Death (FTR§), n (%)	Crude analysis Hazard Ratio (95% CI#)	p	Risk of a complication, n (%)	Death (FTR§), n (%)	Crude analysis Hazard Ratio (95% CI#	p
Superficial wound complication	56 (21)	10 (18)	1.2 (0.6-2.5)	0.5610	25 (28)	10 (40)	2.9 (1.2-7.0)	0.0173
Deep wound complication*	32 (12)	10 (31)	2.3 (1.1-4.7)	0.0193	13 (15)	6 (46)	2.5 (0.9-6.8)	0.0678
Peritonitis	11 (4)	6 (55)	4.7 (2.0-11.0)	0.0004	13 (15)	3 (23)	1.0 (0.3-3.3)	0.9740
Prolonged paralysis	103 (39)	18 (17)	1.0 (0.5-1.8)	0.9240	42 (48)	12 (29)	1.1 (0.5-2.6)	0.8590
GI¤ bleeding	13 (5)	5 (38)	3.3 (1.3-8.3)	0.0115	6 (7)	2 (33)	-	-
Packed blood-products	29 (11)	13 (45)	3.2 (1.7-6.1)	0.0002	18 (20)	8 (44)	2.6 (1.1-5.9)	0.0271
Pneumonia	75 (29)	27 (36)	3.9 (2.3-6.8)	<0.0001	35 (40)	13 (37)	2.3 (1.0-4.9)	0.0386
Cystitis	35 (13)	10 (29)	2.5 (1.3-5.2)	0.0093	9 (10)	1 (11)	-	-
Atrial fibrillation	41 (16)	20 (49)	4.6 (2.6-7.9)	<0.0001	22 (25)	13 (59)	3.4 (1.7-6.8)	0.0008
Pleural exudation	34 (13)	15 (44)	4.5 (2.5-8.3)	<0.0001	28 (32)	11 (39)	2.7 (1.2-6.4)	0.0210
Pulmonary oedema	29 (11)	16 (55)	5.7 (3.2-10.3)	<0.0001	24 (27)	9 (38)	1.8 (0.8-4.2)	0.1410
Respiratory failure	41 (16)	18 (44)	5.2 (2.9-9.1)	<0.0001	27 (31)	11 (41)	2.1 (0.9-4.8)	0.0841
Venous TEEΦ	4 (2)	2 (50)	-	-	2 (2)	0 (0)	-	-
Arterial TEEΦ	10 (4)	5 (50)	4.8 (1.9-12.1)	0.0009	7 (8)	3 (43)	-	-
Renal impairment	17 (7)	10 (59)	9.5 (4.7-19.0)	<0.0001	6 (7)	3 (50)	-	-
Re-operation	55 (21)	16 (29)	2.6 (1.4-4.7)	0.0024	24 (27)	9 (38)	1.7 (0.7-4.0)	0.2050

§ Failure-to-rescue. # Confidence interval. ¤ Gastrointestinal θ *Analysed for laparotomies only, excluding 22 laparoscopic procedures. Φ Thrombo-embolic events. A p-value <0.003 was considered significant.

4 Discussion

We found that a perioperative fluid balance above 2.0–2.5 L was significantly associated with an increased risk of overall and cardiopulmonary complications but not renal, infectious, or wound-related complications. Conversely, a perioperative fluid balance below 0L was not associated with an increased risk of any group of complications. On a continuous scale of fluid balance, the lowest predicted risk of cardiopulmonary complications was found between −1 and 2 L. In comparison, the predicted risk of renal complications increased when the fluid balance rose above 3–3.5 L. Moreover, renal impairment and arterial thromboembolic events were rare, yet most strongly associated with death. Of the more frequent complications, atrial fibrillation, deep wound complications, and respiratory failure were most strongly associated with death. Atrial fibrillation was the only complication associated with death in patients with various pathologies (gastrointestinal obstruction or perforation).

4.1 Fluid balance and the postoperative course

Fluid volume replacement and fluid balance

Our results suggest that patients undergoing emergency gastrointestinal surgery may benefit from a perioperative fluid balance that limits fluid overload. No studies have tested fluid volume replacement strategies in emergency abdominal surgery, while several studies were found for patients undergoing elective surgery.

Brandstrup and colleagues were the first to demonstrate a reduced risk of overall, wound-related, and cardiopulmonary complications from a restrictive perioperative fluid strategy compared with a liberal fluid strategy following elective colorectal surgery.[21] Similar results were found in studies that included patients undergoing various abdominal procedures.[28,29,89] Moreover, studies of patients undergoing urological surgery[130], vascular surgery[131], and mixed surgical procedures[132] (cardiac, trauma, and burn) have reported a reduced number of overall postoperative complications from a restrictive fluid strategy compared with a liberal fluid strategy. Importantly, the studies that demonstrate a positive effect of restrictive fluid administration generally report a positive fluid balance of several litres or a weight gain of several kilograms in the liberal fluid group. In comparison, no difference in postoperative complications or wound infections occurred in three trials following abdominal surgery when comparing a restrictive and a liberal regimen.[85,87,88] In the study by Kalyan and colleagues and Holte and colleagues, a negative body weight change one to two days after surgery was reported in the restrictive fluid group.[87,88] It seems that an intraoperative restrictive fluid strategy benefits from a vigilant postoperative fluid strategy.[31] In all, our

results are comparable with findings in several studies of patients undergoing planned surgery despite differences of patient characteristics with regard to pre-operative state of sepsis, hydration, or bleeding.

On a continuous scale of the fluid balance, we found a U-shaped association with the predicted risk of cardiopulmonary complications in paper I as well as in paper II (Figure 3). As such, our findings endorse the various results in the above-mentioned studies in that the predicted risk of complications seems to increase at a negative as well as a too positive fluid balance. The U-shaped association aligns with results from a meta-analysis and recent cohort study within planned surgery.[133,134]

Our spline models suggest an association between an increased risk of renal complications when the perioperative fluid balance rises above 3 L (Figure 4). Moreover, in paper I a seemingly U-shaped association of perioperative fluid balance and renal complications was found in alignment with the findings of Shin and colleagues.[134] Results that agree with the findings in the largest fluid volume replacement study to date. Myles and colleagues found an increased risk of acute kidney injury in the group receiving a restricted perioperative fluid regimen compared to a liberal fluid regimen (fluid balance 1.4 L vs 3.1 L).[30] The postoperative fluid administration in the restricted group was one of the lowest reported in studies of fluid volume replacement therapy.[21,28,29,85,87,88] Further, postoperative oliguria was allowed and more pronounced in the restrictive fluid group. Nevertheless, a perioperative fluid balance of approximately 3 L seem to be associated with a lower risk of renal complications than did a fluid balance of approximately 1.5 L during high-risk surgery, which supports our findings in emergency surgery (Figure 4).

Goal-directed fluid therapy and the fluid balance

The spline models (Figure 3) suggest a potential perioperative fluid balance optimum of approximately 0 L to 2 L in paper I and −1L to 1L in paper II regarding cardiopulmonary complications. It was surprising that the fluid balance optimum was lower in paper II. One reason might be the overall treatment optimisation in the setup of a randomized clinical trial. Another reason might be the GDT intervention. More patients (59%) receiving the GDT intervention belonged to the Low-FB and Moderate-FB groups in paper II (Table 4). The GAS-ART trial aimed to accommodate hypovolemic events and avoid fluid overload in the GDT-group, which might provide a judicious restrictive fluid strategy, yet not superior to the standard regimen (avoiding fluid overload) in the trial. However, analysing the cohort as a whole (paper II), it seems that the joint benefit from an optimised GDT regimen combined with the avoidance of fluid overload may benefit the postoperative course. We found no increased risk in any group of complications in the Low-FB group in paper II.

Few studies have tested a GDT intervention during emergency abdominal surgery. In the GAS-ART trial we found no significant difference in the composite outcome of postoperative complications and death (preliminary results). In a pilot study, Harten and colleagues found no difference in renal function when randomised 29 patients undergoing emergency abdominal surgery to a GDT regimen compared with a standard regimen.[40] Pavlovic and colleagues enrolled 50 patients who required emergency laparotomy to a calibrated GDT regimen (intervention) or a GDT regimen guided by pulse pressure variation (control).[41] More major complications were found in the intervention group after an interim analysis, probably due to dobutamine administration, and the study was terminated. The two smaller trials have several limitations and confined clinical implications.

Numerous studies have tested the effect of a goal-directed fluid therapy compared with a standard fluid regimen during elective surgery. 'High-risk' patients (mortality risk >5%, high age, or marked co-morbidity/high ASA class) were included in four studies and might resemble patients undergoing emergency surgery. One study found a reduced risk of complications in the GDT group,[38] while two studies found no difference in postoperative complications between a perioperative GDT regimen and a standard regimen.[135,136] The largest study to date found a non-significant reduction of moderate or major complications and mortality at 30 days (absolute risk reduction 6.8%, p=0.07).[95] The pragmatic multicentre setup indicates a benefit from a peri-operative GDT optimisation. In comparison, a Cochrane review found a reduced risk of renal failure, respiratory failure, and wound infections when comparing a GDT intervention with a standard perioperative fluid regimen following planned mixed surgical procedures.[137]

The GDT trials use various setups, GDT-devices, interventions, and the cohorts are diverse. As such, any comparison of study results requires cautious interpretation. Yet, it is remarkable how much the overall fluid administration varies between the GDT trials. In the study by Pestana and colleagues, the intraoperative fluid administration was 2.3 L in the GDT group compared with 5.9 L in the GDT group in the study by Pavlovic and colleagues[41,136] – a difference unlikely explained by the varying study setups. Guidelines recommend a maintenance fluid regimen of 3 ml^{-1} kg^{-1} $hour^{-1}$ during gastrointestinal surgery in an ERAS setting.[138] If we consider a patient of 75 kg undergoing gastrointestinal surgery for 6 hours, only 1.4 L maintenance fluid is needed. As such, it is striking that the fluid administration exceeds more than twice that volume in several GDT trials,[34,139–141] which might increase the risk of interstitial oedema and further the risk of complications.

Sepsis and fluid administration

Pre- and intraoperative sepsis is probably one of the most important reasons for the varying perioperative fluid administration between trials of emergency or 'high-risk' patients. In paper I 15% (51 patients) of the patients had a sepsis-2 score ≥3 (Table2) and in paper II, 6% (18 patients) (Table 4). Since 2001 early resuscitation practise has been enforced in cases of septic shock in the guidelines based on the study by Rivers et al.[19] In contrast, three recent large-scale randomised multicentre trials showed no benefit in 90 day survival from an early resuscitation practice in patients with severe sepsis.[14–16] Importantly, high volume resuscitation (>5 L) of patients with severe sepsis has been associated with an increased risk in mortality.[142] A remarkable alteration in the most recent Surviving Sepsis Campaign guidelines is that the previously forceful goal-directed fluid resuscitation, is now dampened in favour of a more individualised evaluation of the patient's response to the fluid administration. Additionally, it seems that reducing fluid administration after the initial management of sepsis relate to a better outcome.[143] In the light of the optimisation treatment of septichemic patients over the last decades, it seems that a liberal fluid administration in severe sepsis may not yield the same potential as previously and might potentially be harmful.

Confounding by indication

Confounding by indication is probably the most pronounced challenge when addressing the association of perioperative fluid administration and complications in a non-randomised set-up. We found coinciding characteristics in the groups with the most positive perioperative fluid balance in paper I as well as in paper II. The patients had a high sepsis and ASA score, and more patients had gastrointestinal perforation, a greater risk of bowel resection, a longer time of surgery, and were more frequently admitted to the ICU after surgery. All variables are potential confounders and indicate a possible selection bias, with the most ill patients included in the fluid groups with the most positive fluid balance. Conversely, it is striking that the replacement of fluid loss was more than doubled during the perioperative period in the most liberal fluid groups in both papers (Tables 2 and 3), which might have a genuine influence on the risk of complications.

Goal-directed therapy, fluid volume replacement, and fluid balance

Taken together, fluid overload was associated with an increased risk of complications following emergency surgery and suggestions of a similar relation were found from a negative fluid balance. Moreover, the predicted risk of cardiopulmonary and renal complications continued to increase with an increase of fluid balance, indicating that fluid balance may add to an overall optimisation of the perioperative fluid strategy during emergency gastrointestinal surgery. Combining the potential benefits from studies of fluid volume

replacement and GDT trials seems to lower the optimum of the perioperative fluid balance. Multiple variables influence the association between the perioperative fluid therapy, however, and the postoperative course and the effect of a combined restrictive fluid regimen and GDT optimisation is debatable.[144,145] Moreover, due to the setup of the studies, our results are only hypothesis generating and prone to known and unknown confounders.

4.2 Postoperative complications

We found that two-thirds of the overall complications debuted within the first week after surgery (Table 6). Yet, approximately one-third of deep wound complications, re-operations, or pleural exudation evolved between postoperative day 8 to 14, all of which were significantly associated with an increased hazard ratio of death. Similarly, Tengberg and colleagues highlight that postoperative complications arise beyond the immediate postoperative period and stress that a prolonged complex course follows emergency abdominal surgery.[119]

Our findings suggest that recognition and treatment of complications is imperative for weeks after the surgical procedure. Immediate postoperative ICU admittance of the most fragile patients has been argued to optimise the outcome following 'high-risk' abdominal procedures since timely recognition and management of adverse events may be optimised.[3,9,146] However, a randomised clinical trial found no difference in mortality or postoperative complications when allocating patients to a high-dependency unit compared with usual care at the surgical ward after emergency abdominal surgery.[147] In accordance with this finding, a recent prospective cohort study of patients undergoing elective surgery found no evidence that critical care admission directly after surgery was associated with a better risk of survival.[148] As such, immediate postoperative ICU stay may not sufficiently encounter the prolonged complex course following emergency gastrointestinal surgery.[147,148] Future studies are urged to address how to improve the postoperative course for weeks after emergency surgery.

We found that atrial fibrillation, deep wound complications, and respiratory failure were the complications most strongly associated with death in our adjusted analysis (Table 7). A Danish study of patients undergoing emergency colorectal-cancer surgery found that the risk of death was most strongly associated with medical complications (cardiac, pulmonary, infectious, renal, and thromboembolic).[42] Another Danish study found abdominal infection and malfunctioning, pulmonary, and cardiac complications to dominate the postoperative course following emergency gastrointestinal surgery.[119] In an emergency general surgical cohort, McCoy et al. found the strongest association with death for stroke, major bleeding, myocardial

infarction, and pneumonia.[50] In all, various postoperative complications have been associated with an increased risk of death following emergency abdominal surgical procedures.[10,107,149,150]

A striking finding in paper III was that atrial fibrillation uniformly demonstrated a strong association with death in the subgroup of patients with gastrointestinal obstruction as well as perforation (Tables 7 and 8). Atrial fibrillation is generally considered a minor complication and not registered as a complication in several studies. Yet, our findings suggest that atrial fibrillation may serve as an early marker of an adverse postoperative course, in agreement with previous studies.[151,152]

4.3 Clinical implications

Our findings imply that a perioperative fluid balance <2.0 L in the urgent setting may add to an overall optimisation of the perioperative course in patients undergoing emergency gastrointestinal surgery. We found that atrial fibrillation and respiratory failure were among the complications most strongly associated with death. This is an interesting result since a liberal perioperative fluid balance was associated with an increased risk of cardiopulmonary complications of which arrhythmia accounts for approximately one third. Future studies are called for to explore causal relations.

4.4 Randomized clinical trials in the setting of emergency surgery

The initiation and completion of a randomised clinical trials in emergency surgery poses several challenges and may be the reason for limited studies in the field.[153,154] Involvement and consent from patients is challenged by the hectic situation at admission, where concerns about life and death dominate. Moreover, barriers from the treating physicians may be pronounced. In a setting where a myriad of treatment initiatives are offered simultaneously, individual experiences of treatment benefits are likely to influence the physician's decision about 'optimal' treatment and when to enrol a patient in a study ('equipoise').[153] Moreover, the different health care professionals involved in patient treatment are likely to prioritise study-related matters unevenly due to time requirements, competences, or personal benefits (e.g. co-authorships).[154] In comparison, non-randomised trials have implemented multimodal intervention in cohorts of emergency surgical patients.[155–158] However, evaluation of protocol adherence revealed that only selected elements of the intervention were prioritised.[155,158] Dominating reasons were time restraints, lack of structural resources, and the struggles to motivate colleagues.[158] Perioperative fluid optimisation is one defined intervention and might be simpler to implement than a multimodal intervention in patients undergoing emergency surgery. Yet, even during elective surgery, caution about lack of protocol adherence has been called for in studies of perioperative fluid optimisation.[82] Nevertheless, the largest multicentre

RCT to date reports of more than 90% protocol adherence in a population of 'high-risk' abdominal surgical patients.[95]

4.5 Strengths and limitations of study results

The non-randomised study set-up in all three papers challenges deduction about causality, since comparison of the groups in the papers is prone to known and unknow confounders. In paper II the data were originally collected for the randomised clinical trial GAS-ART. However, repealing the randomisation introduces potential confounders in alignment with the retrospective cohort studies. Altogether, our results are hypothesis generating, leaving future randomised clinical trials to explore. Some strengths and limitations need to be addressed explicitly.

4.5.1 The data collection

We extracted data for the retrospective cohort studies by manual assessment, which is probably the most reliable way to extract data from patients records.[102] Retrospective data collection is limited by the data available, which are not registered for study-related matters and are, as such, incoherently reported. Registration of adverse events in the patient file is likely to be inconsistent and based on definitions that vary between physicians. Further, it is likely that registration of complications is recorded in more detail on patients admitted at the ICU than on ward patients. A retrograde classification of complications relies on an interpretation of file data by the data-collector. To accommodate these obstacles, we ensured thorough introduction of data-collectors, pre-defined list of complications, clear definitions of outcome markers, and double assessment of patient records, which were collected in two separate case report forms. Complete data on mortality was ensured by the Danish Civil Registration system.[127]

Prospective data collection allows study-specific variables to be registered and provides unique, high-quality study data. Further, the investigators tend to ensure comprehensive registration of data. Nevertheless, commitment between investigators may vary, which was accommodated for by a thorough teaching of staff and regular meetings with local investigators. Further, clear definitions of variables were used to ensure the uniform registration of data.

Missing data is a noticeable difference between retrospective or prospective data collection. Important variables may not be available in a retrospective study to a degree that forces a change in the study aim. Alternatively, larger proportions of the data may be missing and introduce confounding similar to a selection bias, despite attempts at statistical correction (e.g. imputation). As such, we were pleased to observe that only seven patients were missing fluid data in paper I (Figure 1).

4.5.2 Fluid balance

Intra- and immediate postoperative fluid data were used as exposure in papers I and II, which is challenged by the interdependent fluid administration throughout the entire pre-, intra-, and postoperative period, and all together expected to be associated with the outcome. Yet, the use of intra- and immediate postoperative fluid data as exposure is similar to that of other studies in the field.

Preoperative fluid administration was not available in the retrospective and the prospective study. In the latter, the preoperative fluid data were requested but were, however, incomplete to the extent that did not allow inclusion for fluid balance calculation, the reasons being that fluid data collection was not a standard procedure at the emergency care units at the study sites. Similarly, post-operative fluid data beyond the PACU and ICU stay were not included in paper I since no formal data collection existed beyond that period. Importantly, the electronic anaesthetic database used for fluid data extraction from the intra- and immediate post-operative course, had been used for many years and ensured comprehensive high-quality data. In paper II we included postoperative fluid data until day two due to lack of completeness of data thereafter, which was partly due to free oral intake or toilet visits, and discharge of patients.

We corrected for some known confounders but not for all. We did not adjust for the perioperative blood loss which has been associated with postoperative complications and might have skewed our results.[45,159] However, the difference in blood loss was minimal between the groups in both paper I and II. In papers I and II various types of fluids were administered, but not adjusted for and potentially influencing on renal function.[74,77] The perioperative colloid administration was, however, negligible in the patient groups in paper I. In paper II, a relatively higher dose of Human Albumin was given in the Moderate-FB group, yet was expected to relate minimally to the outcome.[79] Finally, in paper I we did not adjust for the state of sepsis, which is partially included in the ASA classification.[48] We did, however, adjust for the use of vasopressors and performed sensitivity analysis excluding patients with preoperative severe sepsis.

4.5.3 Complications

In papers I and II we grouped complications likely to evolve in continuums and with coincides clinical expression or systemic response. Certain individual complications stand out as the most influential variable in the predefined groups of complications, e.g., the risk of pneumonia was substantially more pronounced than the risk of other infections in the group of infectious complications in paper I as well as in paper II. In paper III, ‘re-operation’ is possibly one of the most diverse groups. It is likely that the various pathologies (e.g. fascial rupture or peritonitis and abscess) influence survival differently.[160] However, the grouping was based on the sound assumption that any re-operation is associated evenly with the postoperative risk of

survival, due to the equally repeated surgical stress response, aesthetical procedure, and perioperative fluid administration.[161] The various risks of individual complications in the predefined groups of complications highlights the need for cautious interpretation of an outcome of grouped complications.

Postoperative complications are associated with several variables.[44,108,159,162] Because of the sample size, it was not possible to adjust for all known confounders, which might have skewed our results in papers I, II, and III. Some co-morbidities were not adjusted for due to lack of available data. Further, we did not grade the severity and number of co-morbidities in each patient, which might have swayed the outcome. However, we did adjust for known important co-morbidities in paper I, the most influential co-morbidities in paper III, and all available co-morbidities in paper II.

The anaesthetic procedure was neither registered nor adjusted for in any paper, but might have influenced the outcome.[163,164] Likewise, postoperative care was not registered, which might have influenced timely recognition and handling of complications, though it is a debatable association. Conversely, we did adjust for the study site (hospitals) in all three papers and thus, indirectly incorporated organisational differences in the analysis.

4.5.4 Prospective randomised trial (paper IV)

The randomised multicentre design in paper IV provides a strong scientific base with several assets. Inclusion criteria were clear, simple, and relevant in a Danish emergency setting. Exclusion criteria were limited to ensure an effective and consecutive enrolment of patients and minimise selection bias. Randomisation was computer generated, with small random blocks blinded for the investigators and project leader to ensure a balanced allocation, which was stratified by hospital and gastrointestinal obstruction or perforation. The perioperative fluid therapy was clearly defined in the intervention and standard care group. We allied ourselves with dedicated trial-physicians to ensure protocol adherence. Moreover, the independent Units of Good Clinical Practice was in charge of the external control to ensure protocol adherences and reduce performance bias. Due to lack of blinding, standardisation of care alongside the intervention was emphasised according to local, regional, and national guidelines to minimise confounding. The primary outcome was clearly defined per-protocol and was patient relevant. Follow-up at 30-days and 90-days postoperative was ensured by the tiral-physicians to minimise attrition bias. Blinded assessment of the primary outcome was planned to minimise detection bias. A thorough plan for data collection, analysis, and presentation of study results was protocolised and in addition published in paper IV to diminish selective reporting and publication bias.

Some limitations were expected. The multimodal handling of patients undergoing emergency gastrointestinal surgery challenges the set-up of a RCT. The urgent nature of the pathology warrants immediate treatment of the patient and restricted time for study-related matters. Thus, the inclusion of the most ill patients may have been restricted due to the limited time to inform the patient and reflection before consent. Consecutive enrolment of patients was challenged by restricting inclusion to the shifts where trial-physicians (project anaesthetics) were present. Furthermore, we were not able to blind enrolled patents, staff, or trial-physicians, which potentially induces performance bias. Finally, interpretation of a composite primary outcome that includes complications and death is challenging. Considering the results in paper I and II outcomes including various complications seems unfortunate when studying the effect of a perioperative fluid strategy. Yet, a composite outcome resembling ours has been used in other studies testing the effect of a perioperative fluid regimen.[95,99]

5 Conclusion

The objective of this thesis was to explore the association between perioperative fluid balance, complications, and death following emergency surgery for gastrointestinal obstruction or perforation.

We found that a perioperative fluid balance above 2.5 L was associated with an increased risk of overall and cardiopulmonary complications in a retrospective cohort study. The predicted risk of cardiopulmonary complications was most favourable for patients with a perioperative fluid balance of 0 L–2 L, whereas a perioperative fluid balance of 1.5–3.5 L was associated with a lower predicted risk of renal complications. The findings were reaffirmed in a similar cohort based on prospectively collected data from the randomised clinical trial 'GAS-ART'. In this study, we found that a perioperative fluid balance above 2.0 L was associated with an increased risk of cardiopulmonary complications and that a potential fluid balance optimum was –1 L to 1 L. In comparison, increase of fluid balance above 3 L was associated with an increase in the predicted risk of renal complications. In both trials background data were skewed, indicating that patients with a more complex pathology occurred in the groups with the highest fluid balance. However, analytical adjustments were performed. Within the limitations of the studies, our results suggest that avoiding fluid overload during emergency gastrointestinal surgery may improve the postoperative course and was associated with a reduced risk of postoperative complications.

We found renal impairment and arterial thromboembolic events to be most strongly associated with death, although infrequent. In the adjusted analysis, atrial fibrillation, deep wound complications, and respiratory failure were most strongly associated with death. Atrial fibrillation was the only complication associated with death in the subgroups of patients with either gastrointestinal obstruction or perforation. Atrial fibrillation may serve as a clinical marker of patients needing escalation of care. Further, we found that the risk of postoperative complications was marked for weeks after the surgical procedure, indicating a prolonged complex course in the cohort.

6 Perspective

The studies presented in this thesis are among the first to explore how perioperative fluid balance is associated with the postoperative course following emergency surgery for gastrointestinal obstruction or perforation and how various complications are associated with death when considering their time of origin. Future trials are encouraged to explore the causal relation between perioperative fluid balance, complications, and death in the patients undergoing emergency surgery.

Our results highlight that perioperative fluid balance should be considered in future trials addressing perioperative fluid optimisation during emergency gastrointestinal surgery as well as in trials studying optimisation by Goal-directed fluid therapy.

We found that perioperative fluid balance associated unevenly with cardiopulmonary and renal complications, which stresses the need to carefully consider outcomes, including various complications, in future trials exploring the effect of fluid optimisation.

In the heterogeneous emergency surgery cohort several studies are called for to address the effect of various elements of fluid optimisation especially their association with different complications. The ongoing FLO-ELA trial will support our understanding[165] but is unlikely to end the disputes about perioperative fluid optimisation in the urgent setting.

Future trials are incited to address treatment optimisation for the weeks after surgery as complications continue to evolve during this period. Focusing on atrial fibrillation as an in-situ marker of patients needing escalation of care is encouraged as it seems to proceed an adverse course.

7 References

1. Voldby AW, Aaen AA, Møller AM, Brandstrup B. Goal-directed fluid therapy in urgent GAstrointestinal Surgery—study protocol for A Randomised multicentre Trial: The GAS-ART trial. *BMJ Open*. 2018;8(11):e022651. doi:10.1136/bmjopen-2018-022651

2. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet*. 2015;385(3):201-209F. doi:10.2471/BLT.15.159293

3. Pearse RM, Harrison DA, James P, et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. *Crit Care*. 2006;10(3):R81. doi:10.1186/cc4928

4. Jhanji S, Thomas B, Ely A, Watson D, Hinds CJ, Pearse RM. Mortality and utilisation of critical care resources amongst high-risk surgical patients in a large NHS trust*. *Anaesthesia*. 2008;63(7):695-700. doi:10.1111/j.1365-2044.2008.05560.x

5. Clarke A, Murdoch H, Thomas MJ, Cook TM, Peden CJ. Mortality and postoperative care after emergency laparotomy. *Eur J Anaesthesiol*. 2011;28:16-19. doi:10.1097/EJA.0b013e32833f5389

6. Ford PNR, Thomas I, Cook TM, Whitley E, Peden CJ. Determinants of outcome in critically ill octogenarians after surgery: an observational study. *Br J Anaesth*. 2007;99(6):824-829. doi:10.1093/bja/aem307

7. Ingraham AM, Cohen ME, Bilimoria KY, et al. Comparison of 30-day outcomes after emergency general surgery procedures: Potential for targeted improvement. *Surgery*. 2010;148(2):217-238. doi:10.1016/j.surg.2010.05.009

8. Saunders DI, Murray D, Pichel AC, Varley S, Peden CJ, UK Emergency Laparotomy Network. Variations in mortality after emergency laparotomy: the first report of the UK Emergency Laparotomy Network. *Br J Anaesth*. 2012;109(3):368-375. doi:10.1093/bja/aes165

9. Symons NRA, Moorthy K, Almoudaris AM, et al. Mortality in high-risk emergency general surgical admissions. *Br J Surg*. 2013;100(10):1318-1325. doi:10.1002/bjs.9208

10. Hentati H, Salloum C, Caillet P, et al. Risk Factors for Mortality and Morbidity in Elderly Patients Presenting with Digestive Surgical Emergencies. *World J Surg*. 2018;42(7):1988-1996. doi:10.1007/s00268-017-4419-3

11. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005;242(3):326-341; discussion 341-3. doi:10.1097/01.sla.0000179621.33268.83

12. Becher RD, Hoth JJ, Miller PR, Mowery NT, Chang MC, Meredith JW. A critical assessment of outcomes in emergency versus nonemergency general surgery using the American College of Surgeons National Surgical Quality Improvement Program database. *Am Surg*. 2011;77(7):951-959. http://www.ncbi.nlm.nih.gov/pubmed/21944366.

13. Rhodes A, Evans LE, Alhazzani W, et al. *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016*. Vol 45. Springer Berlin Heidelberg; 2017. doi:10.1097/CCM.0000000000002255

14. Mouncey PR, Osborn TM, Power GS, et al. Protocolised Management In Sepsis (ProMISe):A multicentre randomised controlled trial of the clinical effectiveness and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock. *Health Technol Assess (Rockv)*. 2015;19(97):1-150. doi:10.3310/hta19970

15. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, et al. Goal-Directed Resuscitation for Patients with Early Septic Shock. *N Engl J Med*. 2014;371(16):1496-1506. doi:10.1056/NEJMoa1404380

16. ProCESS Investigators, Yealy DM, Kellum JA, et al. A Randomized Trial of Protocol-Based Care for Early Septic Shock. *N Engl J Med*. 2014;370(18):1683-1693. doi:10.1056/NEJMoa1401602

17. Lilot M, Ehrenfeld JM, Lee C, Harrington B, Cannesson M, Rinehart J. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. *Br J Anaesth*. 2015;114(5):767-776. doi:10.1093/bja/aeu452

18. Harris B, Schopflin C, Khaghani C, Edwards M, collaborators from the Southcoast Perioperative Audit and Research Collaboration (SPARC). Perioperative intravenous fluid prescribing: a multi-centre audit. *Perioper Med (London, England)*. 2015;4(1):15. doi:10.1186/s13741-015-0025-9

19. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. *N Engl J Med*. 2001;345(19):1368-1377. doi:10.1056/NEJMoa010307

20. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology*. 2008;109(4):723-740. doi:10.1097/ALN.0b013e3181863117

21. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238(5):641-648. doi:10.1097/01.sla.0000094387.50865.23

22. Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. *Br J Anaesth*. 2002;89(4):622-632. doi:https://doi.org/10.1093/bja/aef220

23. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrian BR. Postoperative fluid overload: not a benign problem. *Crit Care Med*. 1990;18(7):728-733. doi:DOI: 10.1097/00003246-199007000-00010

24. Warrillow SJ, Weinberg L, Parker F, et al. Perioperative fluid prescription, complications and outcomes in major elective open gastrointestinal surgery. *Anaesth Intensive Care*. 2010;38(2):259-265. doi:10.1177/0310057x1003800206

25. Cheng AT, Plank LD, Hill GL. Prolonged overexpansion of extracellular water in elderly patients with sepsis. *Arch Surg*. 1998;133(7):745-751. doi:10.1001/archsurg.133.7.745

26. Arieff AI. Fatal postoperative pulmonary edema: pathogenesis and literature review. *Chest*. 1999;115(5):1371-1377. doi:10.1378/chest.115.5.1371

27. Lobo DN, Bostock K a., Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: A randomised controlled trial. *Lancet*. 2002;359:1812-1818. doi:10.1016/S0140-6736(02)08711-1

28. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology*. 2005;103(1):25-32. doi:10.1177/153100350601800129

29. Abraham-Nordling M, Hjern F, Pollack J, Prytz M, Borg T, Kressner U. Randomized clinical trial of fluid restriction in colorectal surgery. *Br J Surg*. 2012;99(2):186-191. doi:10.1002/bjs.7702

30. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. *N Engl J Med*. 2018;378(24):NEJMoa1801601. doi:10.1056/NEJMoa1801601

31. WenKui Y, Ning L, JianFeng G, et al. Restricted peri-operative fluid administration adjusted by serum lactate level improved outcome after major elective surgery for gastrointestinal malignancy. *Surgery*. 2010;147(4):542-552. doi:10.1016/j.surg.2009.10.036

32. Benes J, Chytra I, Altmann P, et al. Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of prospective randomized study. *Crit Care*. 2010;14(3):R118. doi:10.1186/cc9070

33. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg*. 2006;93(9):1069-1076. doi:10.1002/bjs.5454

34. Wakeling HG, McFall MR, Jenkins CS, et al. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth*. 2005;95(5):634-642. doi:10.1093/bja/aei223

35. Salzwedel C, Puig J, Carstens A, et al. Perioperative goal-directed hemodynamic therapy based on radial arterial pulse pressure variation and continuous cardiac index trending reduces postoperative complications after major abdominal surgery: a multi-center, prospective, randomized study. *Crit Care*. 2013;17(5):R191. doi:10.1186/cc12885

36. Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C. Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. *Anaesthesia*. 2002;57(9):845-849. doi:10.1046/j.1365-2044.2002.02708.x

37. Mayer J, Boldt J, Mengistu AM, Röhm KD, Suttner S. Goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized, controlled trial. *Crit Care*. 2010;14(1):R18. doi:10.1186/cc8875

38. Lopes MR, Oliveira M a, Pereira VOS, Lemos IPB, Auler JOC, Michard F. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. *Crit Care*. 2007;11(5):R100. doi:10.1186/cc6117

39. Cecconi M, Corredor C, Arulkumaran N, et al. Clinical review: Goal-directed therapy - what is the evidence in surgical patients ? The effect on different risk groups. *Crit care*. 2013;17:209. doi:10.1186/cc11823

40. Harten J, Crozier JEM, McCreath B, et al. Effect of intraoperative fluid optimisation on renal function in patients undergoing emergency abdominal surgery: A randomised controlled pilot study (ISRCTN 11799696). *Int J Surg*. 2008;6(3):197-204. doi:10.1016/j.ijsu.2008.03.002

41. Pavlovic G, Diaper J, Ellenberger C, et al. Impact of early haemodynamic goal-directed therapy in patients undergoing emergency surgery: an open prospective, randomised trial. *J Clin Monit Comput*. 2016;30(1):87-99. doi:10.1007/s10877-015-9691-x

42. Iversen LH, Bülow S, Christensen IJ, Laurberg S, Harling H. Postoperative medical complications are the main cause of early death after emergency surgery for colonic cancer. *Br J Surg*. 2008;95:1012-1019. doi:10.1002/bjs.6114

43. Al-Temimi MH, Griffee M, Enniss TM, et al. When is death inevitable after emergency laparotomy? Analysis of the american college of surgeons national surgical quality improvement program database. *J Am Coll Surg*. 2012;215(4):503-511. doi:10.1016/j.jamcollsurg.2012.06.004

44. Lee CHA, Kong JCH, Heriot AG, Warrier S, Zalcberg J, Sitzler P. Short-term outcome of emergency colorectal cancer surgery: results from Bi-National Colorectal Cancer Audit. *Int J Colorectal Dis*. September 2018. doi:10.1007/s00384-018-3169-5

45. Matsuyama T, Iranami H, Fujii K, Inoue M, Nakagawa R, Kawashima K. Risk factors for postoperative mortality and morbidities in emergency surgeries. *J Anesth*. 2013;27(6):838-843. doi:10.1007/s00540-013-1639-z

46. Tolstrup M-B, Watt SK, Gögenur I. Morbidity and mortality rates after emergency abdominal surgery: an analysis of 4346 patients scheduled for emergency laparotomy or laparoscopy. *Langenbeck's Arch Surg*. 2017;402(4):615-623. doi:10.1007/s00423-016-1493-1

47. Mistry PK, Gaunay GS, Hoenig DM. Prediction of surgical complications in the elderly: Can we improve outcomes? *Asian J Urol*. 2017;4(1):44-49. doi:10.1016/j.ajur.2016.07.001

48. Barrow E, Anderson ID, Varley S, et al. Current UK practice in emergency laparotomy. *Ann R Coll Surg Engl*. 2013;95(8):599-603. doi:10.1308/rcsann.2013.95.8.599

49. Burmas M, Aitken RJ, Broughton KJ. Outcomes following emergency laparotomy in Australian public hospitals. *ANZ J Surg*. 2018;88(10):998-1002. doi:10.1111/ans.14847

50. McCoy CC, Englum BR, Keenan JE, Vaslef SN, Shapiro ML, Scarborough JE. Impact of specific postoperative complications on the outcomes of emergency general surgery patients. *J Trauma Acute Care Surg*. 2015;78(5):912-919. doi:10.1097/TA.0000000000000611

51. Ingeholm P, on behalf of DCCG. Landsdækkende database for kræft i tyk - og endetarm (DCCG) National årsrapport 2014. 2014:1-182. https://dccg.dk/wp-content/uploads/2017/10/Aarsrapport_2014.pdf.

52. Jørgensen HS, on behalf of AKD. Akut kirurgi databasen. National årsrapport 2017. 2017:1-139.

53. Jørgensen HS, on behalf of AKD. Akut kirurgi databasen. National årsrapport 2014. 2015:1-99.

54. Chana P, Joy M, Casey N, et al. Cohort analysis of outcomes in 69 490 emergency general surgical admissions across an international benchmarking collaborative. *BMJ Open*. 2017;7(3):e014484. doi:10.1136/bmjopen-2016-014484

55. Hatchimonji JS, Kaufman EJ, Sharoky CE, Ma L, Garcia Whitlock AE, Holena DN. Failure to rescue in surgical patients: A review for acute care surgeons. *J Trauma Acute Care Surg*. 2019;87(3):699-706. doi:10.1097/TA.0000000000002365

56. Silber JH, Williams S V., Krakauer H, Schwartz JS. Hospital and patient characteristics associatedwith death after surgery: A study of adverse occurrence and failure to rescue. *Med Care*. 1992;30(7):615-627. doi:10.1097/00005650-199207000-00004

57. Johnston MJ, Arora S, King D, et al. A systematic review to identify the factors that affect failure to rescue and escalation of care in surgery. *Surgery*. 2015;157(4):752-763. doi:10.1016/j.surg.2014.10.017

58. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in Hospital Mortality Associated with Inpatient Surgery. *N Engl J Med*. 2009;361(14):1368-1375. doi:10.1056/NEJMsa0903048

59. Mehta A, Efron DT, Canner JK, et al. Effect of Surgeon and Hospital Volume on Emergency General Surgery Outcomes. *J Am Coll Surg*. 2017;225(5):666-675.e2. doi:10.1016/j.jamcollsurg.2017.08.009

60. Sheetz KH, Dimick JB, Ghaferi AA. Impact of Hospital Characteristics on Failure to Rescue Following Major Surgery. *Ann Surg*. 2016;263(4):692-697. doi:10.1097/SLA.0000000000001414

61. Holena DN, Kaufman EJ, Delgado MK, et al. A metric of our own: Failure to rescue after trauma. *J Trauma Acute Care Surg*. 2017;83(4):698-704. doi:10.1097/TA.0000000000001591

62. Metcalfe D, Castillo-Angeles M, Olufajo OA, et al. Failure to rescue and disparities in emergency general surgery. *J Surg Res*. 2018;231:62-68. doi:10.1016/j.jss.2018.04.047

63. Tajkhorshid E, Nollert P, Jensen MØ, et al. Control of the Selectivity of the Aquaporin Water Channel Family by Global Orientational Tuning. *Science (80-)*. 2002;296(5567):525-530. doi:10.1126/science.1067778

64. Starling EH. On the Absorption of Fluids from the Connective Tissue Spaces. *J Physiol*. 1896;19(4):312-326. http://www.ncbi.nlm.nih.gov/pubmed/16992325. Accessed January 9, 2019.

65. Stevens T, Garcia JGN, Shasby DM, Bhattacharya J, Malik AB. Mechanisms regulating endothelial cell barrier function. *Am J Physiol Cell Mol Physiol*. 2000;279(3):L419-L422. doi:10.1152/ajplung.2000.279.3.L419

66. Chan ST, Kapadia CR, Johnson AW, Radcliffe AG, Dudley HA. Extracellular fluid volume expansion and third space sequestration at the site of small bowel anastomoses. *Br J Surg*. 1983;70(1):36-39. http://www.ncbi.nlm.nih.gov/pubmed/6824880.

67. Chappell D, Bruegger D, Potzel J, et al. Hypervolemia increases release of atrial natriuretic peptide and shedding of the endothelial glycocalyx. *Crit Care*. 2014;18(5):538. doi:10.1186/s13054-014-0538-5

68. Becher RD, Hoth JJ, Miller PR, Meredith JW, Chang MC. Systemic inflammation worsens outcomes in emergency surgical patients. *J Trauma Acute Care Surg*. 2012;72(5):1140-1149. doi:10.1097/TA.0b013e3182516a97

69. McIlroy DR, Kharasch ED. Acute intravascular volume expansion with rapidly administered crystalloid or colloid in the setting of moderate hypovolemia. *Anesth Analg*. 2003;96(6):1572-1577, table of contents. doi:10.1213/01.ANE.0000061460.59320.B0

70. Jacob M, Chappell D, Hofmann-Kiefer K, et al. The intravascular volume effect of Ringer's lactate is below 20%: a prospective study in humans. *Crit Care*. 2012;16(3):R86. doi:10.1186/cc11344

71. Lobo DN, Stanga Z, Aloysius MM, et al. Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: A randomized, three-way crossover study in healthy volunteers. *Crit Care Med*. 2010;38(2):464-470. doi:10.1097/CCM.0b013e3181bc80f1

72. Brandstrup B. Restricted intravenous fluid therapy in colorectal surgery, results of a clinical randomised multi centre trial. *Fac Heal Sci Univ Copenhagen*. 2003;27-6-2003:0-80. doi:10.13140/RG.2.1.4967.2801

73. McCluskey SA, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. *Anesth Analg*. 2013;117(2):412-421. doi:10.1213/ANE.0b013e318293d81e

74. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. *N Engl J Med*. 2018;378(9):829-839. doi:10.1056/NEJMoa1711584

75. Rehm M, Haller M, Orth V, et al. Changes in blood volume and hematocrit during acute preoperative volume loading with 5% albumin or 6% hetastarch solutions in patients before radical hysterectomy. *Anesthesiology*. 2001;95(4):849-856. doi:10.1097/00000542-200110000-00011

76. Hahn RG. Why are crystalloid and colloid fluid requirements similar during surgery and intensive care? *Eur J Anaesthesiol*. 2013;30(9):515-518. doi:10.1097/EJA.0b013e328362a5a9

77. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. *N Engl J Med*. 2012;367(2):124-134. doi:10.1056/NEJMoa1204242

78. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. *N Engl J Med*. 2012;367(20):1901-1911. doi:10.1056/NEJMoa1209759

79. Lewis SR, Pritchard MW, Evans DJWJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev*. 2018;2018(8):CD000567. doi:10.1002/14651858.CD000567.pub7

80. Caironi P, Tognoni G, Masson S, et al. Albumin Replacement in Patients with Severe Sepsis or Septic Shock. *N Engl J Med*. 2014;370(15):1412-1421. doi:10.1056/NEJMoa1305727

81. Yates DRA, Davies SJ, Milner HE, Wilson RJT. Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery. *Br J Anaesth*. 2014;112(2):281-289. doi:10.1093/bja/aet307

82. Joosten A, Delaporte A, Ickx B, et al. Crystalloid versus Colloid for Intraoperative Goal-directed Fluid Therapy Using a Closed-loop System. *Anesthesiology*. 2018;128(1):55-66. doi:10.1097/ALN.0000000000001936

83. Truijen J, Bundgaard-Nielsen M, van Lieshout JJ. A definition of normovolaemia and consequences for cardiovascular control during orthostatic and environmental stress. *Eur J Appl Physiol*. 2010;109(2):141-157. doi:10.1007/s00421-009-1346-5

84. Alpert RA, Roizen MF, Hamilton WK, et al. Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. *Surgery*. 1984;95(6):707-711. http://www.ncbi.nlm.nih.gov/pubmed/6427960.

85. Kabon B, Akça O, Taguchi A, et al. Supplemental intravenous crystalloid administration does not reduce the risk of surgical wound infection. *Anesth Analg*. 2005;101(5):1546-1553. doi:10.1213/01.ANE.0000180217.57952.FE

86. MacKay G, Fearon K, McConnachie A, Serpell MG, Molloy RG, O'Dwyer PJ. Randomized clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. *Br J Surg*. 2006;93(12):1469-1474. doi:10.1002/bjs.5593

87. Holte K, Foss NB, Andersen J, et al. Liberal or restrictive fluid administration in fast-track colonic surgery: a randomized, double-blind study. *Br J Anaesth*. 2007;99(4):500-508. doi:10.1093/bja/aem211

88. Kalyan JP, Rosbergen M, Pal N, et al. Randomized clinical trial of fluid and salt restriction compared with a controlled liberal regimen in elective gastrointestinal surgery. *Br J Surg*. 2013;100(13):1739-1746. doi:10.1002/bjs.9301

89. Gao T, Li N, Zhang J, et al. Restricted Intravenous Fluid Regimen Reduces the Rate of Postoperative Complications and Alters Immunological Activity of Elderly Patients Operated for Abdominal Cancer: A Randomized Prospective Clinical Trail. *World J Surg*. 2012;36(5):993-1002. doi:10.1007/s00268-012-1516-1

90. Patterson SW, Starling EH. On the mechanical factors which determine the output of the ventricles. *J Physiol*. 1914;48(5):357-379. http://www.ncbi.nlm.nih.gov/pubmed/16993262.

91. Jammer I, Tuovila M, Ulvik A. Stroke volume variation to guide fluid therapy: is it suitable for high-risk surgical patients? A terminated randomized controlled trial. *Perioper Med*. 2015;4(1):6. doi:10.1186/s13741-015-0016-x

92. Soop M, Nygren J, Myrenfors P, Thorell A, Ljungqvist O. Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. *Am J Physiol Endocrinol Metab*. 2001;280(4):E576-83. http://www.ncbi.nlm.nih.gov/pubmed/11254464. Accessed March 18, 2016.

93. Henriksen MG, Hessov I, Dela F, Hansen HV, Haraldsted V, Rodt S a. Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery. *Acta Anaesthesiol Scand*. 2003;47(2):191-199. doi:http://dx.doi.org/10.1034/j.1399-6576.2003.00047.x

94. Hausel J, Nygren J, Lagerkranser M, et al. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesth Analg*. 2001;93(5):1344-1350. doi:10.1097/00132586-200304000-00042

95. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA*. 2014;311(21):2181-2190. doi:10.1001/jama.2014.5305

96. Yin K, Ding J, Wu Y, Peng M. Goal-directed fluid therapy based on noninvasive cardiac output monitor reduces postoperative complications in elderly patients after gastrointestinal surgery: A randomized controlled trial. *Pakistan J Med Sci*. 2018;34(6):1320-1325. doi:10.12669/pjms.346.15854

97. Vermeulen H, Hofland J, Legemate D a, Ubbink DT. Intravenous fluid restriction after major abdominal surgery: a randomized blinded clinical trial. *Trials*. 2009;10:50. doi:10.1186/1745-6215-10-50

98. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit Care*. 2005;9(6):R687-93. doi:10.1186/cc3887

99. Gerent ARM, Almeida JP, Fominskiy E, et al. Effect of postoperative goal-directed therapy in cancer patients undergoing high-risk surgery: A randomized clinical trial and meta-analysis. *Crit Care*. 2018;22(1):1-11. doi:10.1186/s13054-018-2055-4

100. Song JW, Chung KC. Observational studies: Cohort and case-control studies. *Plast Reconstr Surg*. 2010;126(6):2234-2242. doi:10.1097/PRS.0b013e3181f44abc

101. Christiaans-Dingelhoff I, Smits M, Zwaan L, Lubberding S, van der Wal G, Wagner C. To what extent are adverse events found in patient records reported by patients and healthcare professionals via complaints, claims and incident reports? *BMC Health Serv Res*. 2011;11:49. doi:10.1186/1472-6963-11-49

102. Ford E, Carroll JA, Smith HE, Scott D, Cassell JA. Extracting information from the text of electronic medical records to improve case detection: a systematic review. *J Am Med Informatics Assoc*. 2016;23(5):1007-1015. doi:10.1093/jamia/ocv180

103. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: New concepts are needed to study research participation effects. *J Clin Epidemiol*. 2014;67(3):267-277. doi:10.1016/j.jclinepi.2013.08.015

104. Nallamothu BK, Hayward RA, Bates ER. Beyond the randomized clinical trial. The role of effectiveness studies in evaluating cardiovascular therapies. *Circulation*. 2008;118(12):1294-1303. doi:10.1161/CIRCULATIONAHA.107.703579

105. Buck DL, Vester-Andersen M, Møller MH. Surgical delay is a critical determinant of survival in perforated peptic ulcer. *Br J Surg*. 2013;100:1045-1049. doi:10.1002/bjs.9175

106. Vester-Andersen M, Lundstrøm LH, Buck DL, Møller MH. Association between surgical delay and survival in high-risk emergency abdominal surgery. A population-based Danish cohort study. *Scand J Gastroenterol*. 2015;5521(June):1-8. doi:10.3109/00365521.2015.1066422

107. McGillicuddy EA, Schuster KM, Davis KA, Longo WE. Factors Predicting Morbidity and Mortality in Emergency Colorectal Procedures in Elderly Patients. *Arch Surg*. 2009;144(12):1157. doi:10.1001/archsurg.2009.203

108. Cook TM, Britton DC, Craft TM, Jones CB, Horrocks M. An audit of hospital mortality after urgent and emergency surgery in the elderly. *Ann R Coll Surg Engl*. 1997;79(5):361-367. http://www.ncbi.nlm.nih.gov/pubmed/9326129.

109. NCEPOD Collaborative. National Confidential Enquiry into Patient Outcome and Death / The NCEPOD Classification of Intervention. https://www.ncepod.org.uk/classification.html.

110. Svenningsen P. Akut Kirurgi Databasen Datadefinitioner. *Reg Klin Kvalitetsudviklingsprogr (RKKP) https//www.rkkp.dk/siteassets/om-rkkp/de-kliniske-kvalitetsdatabaser/akut-kirurgi-databasen/akut-kirurgi-databasen_datadefinitioner_galdende-rev_januar_2019.pdf*. 2019;(version 4.4):1-14.

111. Agresta F, Campanile FC, Podda M, et al. Current status of laparoscopy for acute abdomen in Italy: a critical appraisal of 2012 clinical guidelines from two consecutive nationwide surveys with analysis of 271,323 cases over 5 years. *Surg Endosc*. 2017;31(4):1785-1795. doi:10.1007/s00464-016-5175-4

112. Letarte F, Hallet J, Drolet S, et al. Laparoscopic versus open colonic resection for complicated diverticular disease in the emergency setting: a safe choice? A retrospective comparative cohort study. *Am J Surg*. 2015;209(6):992-998. doi:10.1016/j.amjsurg.2014.07.017

113. Charlson M, Pompei P, Ales K. A New Method of Classifying Prognostic in Longitudinal Studies : Development and Validation. *J Chronic Dis*. 1987;40(5):373-383. http://www.sciencedirect.com/science/article/pii/0021968187901718.

114. Oliver CM, Walker E, Giannaris S, Grocott MPW, Moonesinghe SR. Risk assessment tools validated for patients undergoing emergency laparotomy: A systematic review. *Br J Anaesth*. 2015;115(6):849-860. doi:10.1093/bja/aev350

115. Grocott MPWPW, Browne JPP, Van der Meulen J, et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *J Clin Epidemiol*. 2007;60(9):919-928. doi:10.1016/j.jclinepi.2006.12.003

116. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae

117. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013;258(1):1-7. doi:10.1097/SLA.0b013e318296c732

118. Brandstrup B, Svendsen PE, Rasmussen M, et al. Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance? *Br J Anaesth*. 2012;109(June):191-199. doi:10.1093/bja/aes163

119. Tengberg LT, Cihoric M, Foss NB, et al. Complications after emergency laparotomy beyond the immediate postoperative period - a retrospective, observational cohort study of 1139 patients. *Anaesthesia*. 2017;72(3):309-316. doi:10.1111/anae.13721

120. Mentula PJ, Leppäniemi AK. Applicability of the Clavien-Dindo classification to emergency surgical procedures: a retrospective cohort study on 444 consecutive patients. *Patient Saf Surg*. 2014;8(1):31. doi:10.1186/1754-9493-8-31

121. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1(1):43-46. doi:10.1097/00001648-199001000-00010

122. Ottenbacher KJ. Quantitative evaluation of multiplicity in epidemiology and public health research. *Am J Epidemiol*. 1998;147(7):615-619. doi:10.1093/oxfordjournals.aje.a009501

123. Perneger T V. What's wrong with Bonferroni adjustments. *Br Med J*. 1998;316(7139):1236-1238. doi:10.1136/bmj.316.7139.1236

124. Armstrong RA. When to use the Bonferroni correction. *Ophthalmic Physiol Opt*. 2014;34(5):502-508. doi:10.1111/opo.12131

125. Moyé LA. P-value interpretation and alpha allocation in clinical trials. *Ann Epidemiol*. 1998;8(6):351-357. doi:10.1016/S1047-2797(98)00003-9

126. Senagore AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. *Clin Exp Gastroenterol*. 2010;3(1):87-89. doi:10.2147/ceg.s4243

127. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7_suppl):22-25. doi:10.1177/1403494810387965

128. Watt DG, Wilson MSJ, Shapter OC, Patil P. 30-Day and 1-year mortality in emergency general surgery laparotomies: an area of concern and need for improvement? *Eur J Trauma Emerg Surg*. 2014;41(4):369-374. doi:10.1007/s00068-014-0450-3

129. Pöpping DM, Elia N, Marret E, Remy C, Tramèr MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. *Arch Surg*. 2008;143(10):990-999; discussion 1000. doi:10.1001/archsurg.143.10.990

130. Wuethrich PY, Burkhard FC, Thalmann GN, et al. Restrictive deferred hydration combined with preemptive norepinephrine infusion during radical cystectomy reduces postoperative complications and hospitalization time. *Anesthesiology*. 2014;120(2):365-377. doi:http://dx.doi.org/10.1097/ALN.0b013e3182a44440

131. McArdle GT, McAuley DF, McKinley A, Blair P, Hoper M, Harkin DW. Preliminary results of a prospective randomized trial of restrictive versus standard fluid regime in elective open abdominal aortic aneurysm repair. *Ann Surg*. 2009;250(1):28-34. doi:10.1097/SLA.0b013e3181ad61c8

132. Stewart RM, Park PK, Hunt JP, et al. Less Is More: Improved Outcomes in Surgical Patients with Conservative Fluid Administration and Central Venous Catheter Monitoring. *J Am Coll Surg*. 2009;208(5):725-735. doi:10.1016/j.jamcollsurg.2009.01.026

133. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. *Proc Nutr Soc*. 2010;69(4):488-498. doi:10.1017/S0029665110001734

134. Shin CH, Long DR, McLean D, et al. Effects of Intraoperative Fluid Management on Postoperative Outcomes. *Ann Surg*. March 2017:1. doi:10.1097/SLA.0000000000002220

135. Scheeren TWL, Wiesenack C, Gerlach H, Marx G. Goal-directed intraoperative fluid therapy guided by stroke volume and its variation in high-risk surgical patients: A prospective randomized multicentre study. *J Clin Monit Comput*. 2013;27:225-233. doi:10.1007/s10877-013-9461-6

136. Pestaña D, Espinosa E, Eden A, et al. Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: a prospective, randomized, multicenter, pragmatic trial: POEMAS Study (PeriOperative goal-directed thErapy in Major Abdominal Surg. *Anesth Analg*. 2014;119(3):579-587. doi:10.1213/ane.0000000000000295

137. Grocott MP, Dushianthan A, Hamilton MA, et al. Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery. *Cochrane Database Syst Rev*. 2012;11:CD004082. doi:10.1002/14651858.CD004082.pub5

138. Feldheiser A, Aziz O, Baldini G, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: Consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand*. 2016;60(3):289-334. doi:10.1111/aas.12651

139. Challand C, Struthers R, Sneyd JR, et al. Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. *Br J Anaesth*. 2012;108(1):53-62. doi:10.1093/bja/aer273

140. Buettner M, Schummer W, Huettemann E, Schenke S, Van Hout N, Sakka SG. Influence of systolic-pressure-variation-guided intraoperative fluid management on organ function and oxygen transport. *Br J Anaesth*. 2008;101(2):194-199. doi:10.1093/bja/aen126

141. Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology*. 2002;97(4):820-826. doi:10.1097/00000542-200210000-00012

142. Marik PE, Linde-Zwirble WT, Bittner EA, Sahatjian J, Hansell D. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. *Intensive Care Med*. 2017;43(5):625-632. doi:10.1007/s00134-016-4675-y

143. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med*. 2016;42(11):1695-1705. doi:10.1007/s00134-016-4500-7

144. Futier E, Constantin J-M, Petit A, et al. Conservative vs restrictive individualized goal-directed fluid replacement strategy in major abdominal surgery: A prospective randomized trial. *Arch Surg*. 2010;145(12):1193-1200. doi:10.1001/archsurg.2010.275

145. Lobo SM, Ronchi LS, Oliveira NE, et al. Restrictive strategy of intraoperative fluid maintenance during optimization of oxygen delivery decreases major complications after high-risk surgery. *Crit Care*. 2011;15(5):R226. doi:10.1186/cc10466

146. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: A 7 day cohort study. *Lancet*. 2012;380(9847):1059-1065. doi:10.1016/S0140-6736(12)61148-9

147. Vester-Andersen M, Waldau T, Wetterslev J, et al. Randomized multicentre feasibility trial of intermediate care versus standard ward care after emergency abdominal surgery (InCare trial). *Br J Surg*. 2015;102(6):619-629. doi:10.1002/bjs.9749

148. Kahan BC, Koulenti D, Arvaniti K, et al. Critical care admission following elective surgery was not associated with survival benefit: prospective analysis of data from 27 countries. *Intensive Care Med*. 2017;43(7):971-979. doi:10.1007/s00134-016-4633-8

149. Howes TE, Cook TM, Corrigan LJ, Dalton SJ, Richards SK, Peden CJ. Postoperative morbidity survey, mortality and length of stay following emergency laparotomy. *Anaesthesia*. 2015;70(9):1020-1027. doi:10.1111/anae.12991

150. Merani S, Payne J, Padwal RS, et al. Predictors of in-hospital mortality and complications in very elderly patients undergoing emergency surgery. *World J Emerg Surg*. 2014;9(1):43. doi:10.1186/1749-7922-9-43

151. Wells CI, Robertson JP, Campbell S, Al-Herz F, Rhind B, Young M. Impact of atrial fibrillation on long-term survival following oesophagectomy: a 21-year observational study. *ANZ J Surg*. 2018;88(4):E268-E272. doi:10.1111/ans.14054

152. Bhave PD, Goldman LE, Vittinghoff E, Maselli J, Auerbach A. Incidence, predictors, and outcomes associated with postoperative atrial fibrillation after major noncardiac surgery. *Am Heart J*. 2012;164(6):918-924. doi:10.1016/j.ahj.2012.09.004

153. Perry DC, Griffin XL, Parsons N, Costa ML. Designing clinical trials in trauma surgery. *Bone Joint Res*. 2014;3(4):123-129. doi:10.1302/2046-3758.34.2000283

154. Coats TJ. Barriers, regulations and solutions in emergency surgery research. *Br J Surg*. 2014;101(1):3-4. doi:10.1002/bjs.9327

155. Huddart S, Peden CJ, Swart M, et al. Use of a pathway quality improvement care bundle to reduce mortality after emergency laparotomy. *Br J Surg*. 2015;102:57-66. doi:10.1002/bjs.9658

156. Tengberg LT, Bay-Nielsen M, Bisgaard T, et al. Multidisciplinary perioperative protocol in patients undergoing acute high-risk abdominal surgery. *Br J Surg*. 2017;104(4):463-471. doi:10.1002/bjs.10427

157. Møller MH, Adamsen S, Thomsen RW, Møller AM, Peptic Ulcer Perforation (PULP) trial group. Multicentre trial of a perioperative protocol to reduce mortality in patients with peptic ulcer perforation. *Br J Surg*. 2011;98(6):802-810. doi:10.1002/bjs.7429

158. Stephens TJ, Peden CJ, Pearse RM, et al. Improving care at scale: process evaluation of a multi-component quality improvement intervention to reduce mortality after emergency abdominal surgery (EPOCH trial). *Implement Sci*. 2018;13(1):142. doi:10.1186/s13012-018-0823-9

159. Sørensen LT, Malaki A, Wille-Jørgensen P, et al. Risk factors for mortality and postoperative complications after gastrointestinal surgery. *J Gastrointest Surg*. 2007;11(7):903-910. doi:10.1007/s11605-007-0165-4

160. Almoudaris AM, Burns EM, Mamidanna R, et al. Value of failure to rescue as a marker of the standard of care following reoperation for complications after colorectal resection. *Br J Surg*. 2011;98(12):1775-1783. doi:10.1002/bjs.7648

161. Guevara OA, Rubio-Romero JA, Ruiz-Parra AI. Unplanned reoperations: is emergency surgery a risk factor? A cohort study. *J Surg Res*. 2013;182(1):11-16. doi:10.1016/j.jss.2012.07.060

162. Awad S, Herrod PJJ, Palmer R, et al. One-and two-year outcomes and predictors of mortality following emergency laparotomy: A consecutive series from a united kingdom teaching hospital. *World J Surg*. 2012;36(9):2060-2067. doi:10.1007/s00268-012-1614-0

163. Abbott TEF, Pearse RM, Archbold RA, et al. A Prospective International Multicentre Cohort Study of Intraoperative Heart Rate and Systolic Blood Pressure and Myocardial Injury After Noncardiac Surgery. *Anesth Analg*. 2018;126(6):1936-1945. doi:10.1213/ANE.0000000000002560

164. McLean DJ, Diaz-Gil D, Farhan HN, Ladha KS, Kurth T, Eikermann M. Dose-dependent Association between Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications. *Anesthesiology*. 2015;122(6):1201-1213. doi:10.1097/ALN.0000000000000674

165. Edwards MR. Flow optimisation in emergency laparotomy. FLO-ELA trial. https://www.floela.org/home.

8 Appendix

10.1 Paper I

10.2 Paper II

10.3 Paper III

10.4 Paper IV

8.1 Paper I

Peri-operative Fluid Administration and Complications in Emergency Gastrointestinal Surgery – an Observational Study

Title: Peri-operative Fluid Administration and Complications in Emergency Gastrointestinal Surgery – an Observational Study

Short running title: Fluid therapy in emergency surgery, complications

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Previous presentation of results

Preliminary study results were presented at the annually meeting at the Danish Surgical Society in the fall of 2019.

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Abstract

Background: The fluid balance associated with a better outcome following emergency surgery is unknown. The aim of this study was to explore the association of the peri-operative fluid balance and post-operative complications during emergency gastrointestinal surgery.

Methods: We retrospectively included patients undergoing emergency surgery for gastrointestinal obstruction or perforation. A peri-operative fluid balance of 2.5L divided the cohort in a conservative and liberal group. Outcome was Clavien-Dindo graded complications registered 90 days post-operatively. We used logistic regression adjusted for age, sex, American Society of Anesthesiologists' classification, use of epidural analgesia, use of vasopressor, type of surgery, intraabdominal pathology, and hospital. Predicted risk of complications was demonstrated on a continuous scale of the fluid balance.

Results: We included 342 patients operated between July 2014 and July 2015 from three centers. The peri-operative fluid balance was 1.6L IQR [1.0 to 2.0] in the conservative vs. 3.6L IQR [3.0 to 5.3] in the liberal group. Odds ratio of overall 2.6 (95% CI 1.5 to 4.4), $p<0.001$ and cardiopulmonary complications 3.2 (95% CI 1.9 to 5.7), $p<0.001$ was increased in the liberal group. A peri-operative fluid balance of 0-2L was associated with minimal risk of cardiopulmonary complications compared to 1.5-3.5L for renal complications.

Conclusion: We found a peri-operative fluid balance above 2.5L to be associated with an increased risk of overall and cardiopulmonary complications following emergency surgery for gastrointestinal obstruction or perforation. A peri-operative fluid balance of 0-2 liters was associated with the lowest risk of cardiopulmonary complications and 1.5-3.5 liters for renal complications.

Key points summary:

- We aimed to study the effect of a peri-operative fluid balance above 2.5L on postoperative complications following emergency gastrointestinal surgery.
- We found that a peri-operative fluid balance above 2.5L was significantly associated with an increased risk of overall and cardiopulmonary complications and that the predicted risk of cardiopulmonary complications was at a minimum at a peri-operative fluid balance between 0-2L compared to 1.5-3.5L for renal complications.
- Our results, from this multicenter observational study, imply a clinical potential of an optimized peri-operative fluid strategy in patients undergoing emergency gastrointestinal surgery.

Introduction

Worldwide, more than 310 million patients undergo major surgery each year.[1] Mortality and complication rates are among the highest in patients undergoing emergency gastrointestinal surgery.[2,3] Peri-operative intravenous fluid is given to replace fluid loss and to ensure the perfusion of the organs. However, escape to the extravascular space rapidly diminishes the circulatory effect. Interstitial edema may follow and counteract tissue oxygenation. Systemic sepsis and the trauma of surgery might further amplify the extravascular escape of intravenous fluids. Little is known about which fluid strategy that is associated with a better outcome during emergency gastrointestinal surgery.

Studies comparing a restrictive and a liberal fluid strategy in patients undergoing elective abdominal surgery have shown that a restrictive strategy reduces the risk of complications and length of hospital stay.[4–6] Yet, a too restrictive fluid strategy may cause renal failure.[7] A zero-balance approach has been shown to reduce cardiopulmonary and tissue healing complications in elective abdominal surgery.[8] Based on these findings, programs of Enhanced Recovery After Surgery (ERAS) recommend a conservative peri-operative fluid approach and a weight gain of no more than 2.5 kg.[9] Patients undergoing emergency gastrointestinal surgery may benefit from a similar restrictive peri-operative fluid approach.

The pathophysiological differences between patients undergoing elective and emergency surgery are marked. Patients undergoing emergency surgery are usually older, have more co-morbidities, and post-operative complications and death are more frequent than in patients undergoing elective surgery.[10,11] The peri-operative fluid strategy is often challenged by pre-operative deterioration of the patient. Periods with reduced fluid intake, excessive pathological fluid losses (e.g. vomiting), and a hyper-inflammatory state call for careful attention when administering intravenous fluids.[12] Sepsis may accompany the condition and fluid administration is a key element in the treatment. However, the volume associated with a better outcome is uncertain, especially for the surgical patient with sepsis.[13–16]

We hypothesized that a peri-operative liberal fluid strategy increases the risk of complications following emergency surgery for gastrointestinal obstruction or perforation. The aim of this cohort study was to compare the association of a conservative and a liberal fluid balance with post-operative complications following emergency surgery for gastrointestinal obstruction or perforation, and subsequently study the influence of the peri-operative fluid balance on each type of complication.

Methods

Study approval was granted by the Danish Patient Safety Authority (3-3013-1999/1) and the Danish Data Protection Agency (REG-149-2016) prior to data extraction. Ethical approval for this study (J.nr. 16-000014) was provided by the Ethical Committee, Zealand Region, Denmark on 14 December 2016. The requirement for written informed consent was waived by the committee. We retrospectively collected data on patients admitted between 1 July 2014 and 31 July 2015 at three teaching hospitals in Denmark between June 15 2017 and 31 March 2018. The study sites offer treatment free of charge for a population of approximately 800,000 citizens. Local guidelines for intra-operative fluid administration during emergency gastrointestinal surgery were not present during the study period. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement was used in drafting this manuscript.[17]

We included all adult Danish residents undergoing emergency gastrointestinal surgery due to obstruction or perforation confirmed radiologically. Minor surgical procedures such as appendectomies, cholecystectomies, and endoscopic procedures were excluded. We defined emergency surgery as any intraabdominal procedure without planned delay. We excluded children (aged 17 years or younger), pregnant women, patients receiving regular dialysis, or patients with a traumatic or iatrogenic perforation. If eligible for inclusion more than once patients were included only at the first procedure. We excluded patients who had had intraabdominal surgery 30 days prior to eligibility or patients without data on the intra- and post-operative fluid therapy. The Danish Civil Registration System provides uniform identification of every citizen through a personal identification number used to access all electronically stored medical and anesthetic records. It offers complete information on death for all Danish residents.[18]

The primary exposure was the peri-operative fluid balance starting from the induction of anesthesia and to the end of stay at the post-anesthetic care unit or the intensive care unit (ICU) for up to 24 hours. Fluid administration included: crystalloids, glucose-containing fluids, colloids, intravenous drugs, packed blood products, and per oral intake. Fluid loss included diuresis, aspiration, emptied ascites, blood loss, and perspiration calculated as 0.5 mL kg^{-1} $hour^{-1}$. The fluid balance was calculated as the difference between the fluid administration and the fluid loss. Patients were divided in a conservative and liberal group at a peri-operative fluid balance of 2.5L in alignment with the ERAS recommendations.[19]

The primary outcome was complications until post-operative day 90. The Clavien-Dindo classification (CDC)[20] graded the complications and they were grouped into overall, wound-related, cardiopulmonary, renal, or infectious. We omitted CDC grade 1 because we expected nearly all patients to have a grade 1

complication. A complication graded CDC ≥ 3 was defined as a major complication and required radiological, endoscopic, or surgical intervention or critical care; which we defined as an admission at the intensive care unit. Secondary outcome was major complications or death at post-operative day 90.

We registered the post-operative complications as follows: wound-related complications included superficial wound rupture, rupture of the fascia, or anastomotic leakage. Cardiopulmonary complications included cardiac arrhythmia, acute myocardial infarction, cardiac arrest, pleural effusion, pulmonary congestion, pulmonary edema, congestive heart failure, or respiratory failure (failure to wean >48 hours, requiring continuous positive airway pressure after the day of extubating, or re-intubation of any cause). Renal complications included the need for dialysis or other renal complications (nephritis or hydronephrosis treated with a nephrostomy catheter). Infectious complications included superficial wound infection, pneumonia, urinary tract infection, or cutaneous infection.

The three participating hospitals used identical software and uniform registration of variables. We screened the booking system for patients undergoing abdominal surgery. All emergency procedures meeting the inclusion criteria and unclassified cases were further explored. We accessed the medical and anesthetic records on each patient eligible for inclusion. The data collected pre-operatively were physiological status, co-morbidities, sepsis-2 score, and American Society of Anesthesiologists' (ASA) classification. Intra-operatively we registered the fluid administration and loss as specified above, vasopressor use and dose, hypotensive episodes defined as mean arterial pressure <50 mm Hg at any time intra- and post-operatively, and the use of epidural analgesia.

Case report forms were used for data collection by our medically trained team. All team members were trained in the use of the Clavien-Dindo classification. AAA and AWV collected anesthetic data, fluid administration, and losses. Two independent team members assessed each patient file and registered data on complications in two separate case report forms. Regular audit by the project leader (AWV) corrected irregularities. The senior advisor (BB) was consulted in case of incongruity. Database entry was conducted twice and inconsistencies were corrected by revisiting the case report form.

Statistics

Data were tested for normality and parametric or non-parametric statistics was used as appropriate. The primary outcome was analyzed with multiple logistic regression. Confounders included were settled between the authors and a statistician based on a priori knowledge of variables known to be associated

with the fluid administration by the physician and the post-operative complications. [21,22] We included sex, age, ASA class (grouped at I-II or III-V), use of epidural analgesia (yes or no), use of vasopressors (yes or no), the type of surgery performed (bowel resection, other procedure, or palliative surgery (exculpatory stoma formation or limited treatment)), the intraabdominal pathology (gastrointestinal obstruction or perforation), and the hospital (Holbæk, Slagelse, or Køge). Age were left skewed and the potency was used. In case of >5% missing data of independent variables multiple imputation was planned. We performed a subgroup analysis excluding patients with pre-operative sepsis-2-score ≥3 or those admitted directly to the ICU after surgery. Additionally, we analyzed patients with major complications separately. The results are presented as odds ratio (OR) with 95% confidence interval (95% CI). Statistically significance was Bonferroni corrected based on five outcomes, thus defined by a two-sided p-value <0.01. We presented the predicted risk of complications depending on the fluid balance on a continuous scale. A generalized additive model with smoothing splines and four degrees of freedom was used. The statistical plan was approved by the authors before commencing the analyzing of data. The statistical software was R version 3.5.0 GUI 1.70 El Capitan ©R, 2016 and RStudio version 1.1.453.

Results

A total of 457 patients had emergency surgery with radiologically verified GI obstruction or perforation and were screened for inclusion. Of these, 342 patients were eligible for inclusion. Excluded were five patients because of pregnancy or age below 18 years, one had end-stage renal failure, 65 patients had GI surgery within 30 days before the index procedure, fifteen had an iatrogenic perforation, nine patients had already been included once, eleven patients had trauma surgery, two patients were of foreign nationality, and seven patients were missing fluid data from the peri-operative period.

A peri-operative fluid balance of 2.5L divided the cohort in two groups of similar size (table 1). More patients in the liberal group had a gastrointestinal perforation (54 (33%) vs. 30 (17%)). In agreement with this more patients in the liberal group had a pre-operative sepsis score of 3-4 (36 (22%) vs. 15 (9%)), an ASA score of III-V (86 (53%) vs. 69 (39%)), and were more frequently admitted to the ICU directly following surgery (53 (33%) vs. 15 (8%)).

During surgery, the liberal group had more hypotensive episodes, yet patients receiving vasopressor treatment were comparable between the groups. Post-operatively, more patients had hypotensive episodes and received vasopressors in the liberal group (table 2). The median [IQR] peri-operative fluid balance was 1.6L IQR [1.0 to 2.0] in the conservative group and 3.6L [3.0 to 5.3] in the liberal group (table 2). The liberal group were given more fluid intra- and post-operatively, however the fluid loss increased primarily due to increase in diuresis.

Primary outcome

Altogether, 225 (65.8%) patients had complications. The overall risk of complications was significantly associated with the liberal fluid group with an adjusted OR of 2.6 (95% CI 1.5 to 4.4), $p<0.001$ (Table 3). No data were missing of the independent variables in the regression model. Subgroup analysis revealed a significantly increased risk of cardiopulmonary complications, OR: 3.2 (95% CI 1.9 to 5.7), $p<0.001$ in the liberal group.

The association between the predicted risk of complications and the peri-operative fluid balance on a continuous scale is presented in Figure 1-3 and Supplementary Figure 1 and 2. The figures show that an increased peri-operative fluid balance is associated with an increased risk of overall, cardiopulmonary, renal, or infectious complications. A U-shaped association between the peri-operative fluid balance and the predicted risk of cardiopulmonary or renal complications is a good fit. The predicted risk of a

cardiopulmonary complication is at a minimum at a peri-operative fluid balance approximating 0-2L, whereas the minimal risk of renal complications is at a fluid balance approximating 1.5-3.5L.

Major complications and death

A total of 111 (32.5%) patients developed a major complication (CDC≥3). The risk of a major complication was not significantly associated with the liberal group (OR 1.6 (95% CI 1.0 to 2.7), p=0.077), Table 3. However, the association between the predicted risk of a major complications and the peri-operative fluid balance on a continuous scale showed a U-shaped relation suggesting an optimal fluid balance of approximately 1-3L (Supplementary Figure 3). The overall risk of death was 25.4%. The risk of death was not associated with the peri-operative fluid balance.

Sensitivity analysis

We analyzed our data after excluding the 51 patients with a pre-operative sepsis score of 3-4 and three patients of which data were missing. The risk of complications remained largely unchanged (Supplementary Table 1). Likewise, analyzing the data without the 68 patients admitted to the ICU immediately after surgery did not change the risk of complications (Supplementary Table 2). Of the patients admitted directly to the ICU after surgery 31 had a pre-operative sepsis score of 3-4 and 29 had post-operative hypotensive episodes of which 24 belonged to the liberal fluid group.

Discussion

Our study of patients undergoing emergency surgery for gastrointestinal obstruction or perforation showed a peri-operative fluid balance of 3.6L IQR [3.0 to 5.3] compared with 1.6L IQR [1.0, to 2.0] to be significantly associated with a higher risk of post-operative complications, especially cardiopulmonary complications. The correlation remained robust after the exclusion of patients with pre-operative severe sepsis or patients directly admitted at the ICU following surgery. The predicted risk of cardiopulmonary and major complications were at a minimum at a peri-operative fluid balance of 0-2 liters, whereas the predicted risk of renal complications were at a minimum at a fluid balance of 1.5-3.5 liters.

Little is known about the influence of the peri-operative fluid therapy on post-operative complications in patients undergoing emergency gastrointestinal surgery. One pilot study randomized 29 patients undergoing emergency abdominal surgery to two different fluid strategies.[23] The peri-operative fluid balance was 2.1L vs 2.9L. No difference in renal function was found. In an early terminated study, 50 patients with severe sepsis undergoing mixed emergency surgery were randomized to two different goal directed fluid strategies.[24] The crystalloid administration was 5.6L vs 5.9L (control vs optimized). A significant increase in cardiac complications was found in the optimized group, most likely due to the protocolized dobutamine administration. We found more cardiopulmonary complications in the patients given a liberal fluid therapy. The group also received more vasopressors post-operatively. The dominating drug given was norepinephrine, which for most parts was given in the intensive care unit. Even so, our result remained robust in the sensitivity analysis when excluding patients directly admitted to the intensive care unit. This indicates that cardiopulmonary complications are not related to the greater use of vasoactive drugs in the liberal group in our study.

We demonstrated a U-shaped correlation between the fluid balance and post-operative complications. This has previously been suggested in meta-analysis of studies comparing restrictive vs. liberal fluid strategies during elective abdominal surgery.[25,26] Some studies show a positive result from a restrictive peri-operative fluid strategy[4,6,8] while others report no effect or even a negative effect of a restrictive peri-operative fluid strategy.[27–29] The varying results may relate to the circumstance that a ‘restrictive` peri-operative fluid strategy in one study might resemble a ‘liberal` fluid strategy in another study and that different groups of complications are used as outcome.[28,30]

Our results suggest that the risk of cardiopulmonary and renal complications are differently associated with the peri-operative fluid balance. Findings in agreement with a registry study of patients admitted for

elective non-cardiac surgery. Shin and colleagues included 92,000 patients in the study and divided the group in quintiles according to the fluid administration. They found a peri-operative fluid administration of >2.7L to be significantly associated with an increased risk of respiratory complications, acute kidney injury, and mortality at 30 days.[31] Additionally, a too restrictive peri-operative fluid administration of ≤0.9L was associated with an increased risk of acute kidney injury, thus suggesting a U-shaped correlation between the fluid administration and the incidence of complications. The study implies a more beneficial outcome in the group of patients receiving a peri-operative fluid infusion of 6-7 mL kg^{-1} $hour^{-1}$. In similarity, we found a more favorable outcome of a peri-operative fluid balance of 1.6L comparable to a fluid administration of 5.9 mL kg^{-1} $hour^{-1}$ for overall and cardiopulmonary complications. Our data suggest that renal function might benefit from a greater fluid administration, and are supported by the study including the largest number of elective surgical patients randomized to a liberal versus restricted fluid strategy: more patients with renal failure were found in the restricted group. Noteworthy, the protocol for that trial did not recommend fluid administration to patients with post-operative oliguria.[7]

The limitations of our study lay within the retrospective design. More patients in the liberal group had gastrointestinal perforation with sepsis and a high ASA score. We chose to adjust for the ASA score. Severe sepsis and co-morbidities are both inherent in the ASA score and as such dependent variables. The use of vasopressors was adjusted for in the regression model. We did, however, not distinguish between different vasoactive drugs, nor a single- versus continuous administration. Blood loss, hypotension, and sepsis are likely to prompt fluid administration but are also linked with increase in morbidity which challenge interpretation of study results.[32–34] However, the sensitivity analysis excluding the patients with pre-operative severe sepsis did not change the result, and the difference in blood loss between the groups was minimal (table 2). We did not register and include the anesthesia used in our analysis.[35] The anesthetists from the participating hospitals use for most parts Propofol, Remifentanil and if indicated Rocuronium. Our fluid data relied on the intra- and immediate post-operative period, but not the pre-operative or later post-operative period. This is in accordance with most studies in the field.

The strengths of our study are the detailed prospectively registered record-data of peri-operative fluid administration. Our data included fluid given as iv-medicine which is often omitted in other studies. Further, double registration of the fluid data and complications was performed to ensure the completeness of available data and avoid misclassification of complications. We adjusted for known confounders influencing the fluid administration and the post-operative complications, further strengthening our findings.

Our results imply a clinical potential of an optimized peri-operative fluid strategy in patients undergoing emergency gastrointestinal surgery. The multicenter design strengthens external validity of the study results. Yet, the design has inherent limitations and causal relations are for future trials to explore.

Conclusion

We found a peri-operative fluid balance above 2.5L to be significantly associated with an increased risk of overall and cardiopulmonary complications following emergency surgery for gastrointestinal obstruction or perforation. The predicted risk of complications demonstrates a U-shaped correlation with the peri-operative fluid balance. A peri-operative fluid balance of 0-2L was associated with the fewest cardiopulmonary complications. The equivalent estimate was 1.5-3.5L for renal complications. Our findings support our thesis that avoiding fluid overload in patients undergoing emergency gastrointestinal surgery may reduce the risk of complications.

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Previous presentation of study results

Preliminary study results have been presented at the Danish Surgical Society Annual Meeting 2019.

Keywords:

Fluid therapy, intestinal obstruction, intestinal perforation, intra-operative care, post-operative complications

Glossary of Terms

ASA:	American Society of Anesthesiologists' physical status classification
CDC:	Clavien-Dindo classification
CI:	Confidence interval
ICU:	Intensive care unit
IQR:	Interquartile range
OR:	Odds ratio

Authors' contributions

Anders Voldby: This author designed the idea, outlined the protocol, obtaining legislative and ethical approvals, planned the study, searched the literature, collected the data, planned and conducted the analysis, interpreted the results, drafted the present manuscript, and raised the funds.
Anne Aaen: This author collected the data, revised the analysis and interpretation, and revised the manuscript.
Jakob Burcharth: This author collected the data, revised the analysis and interpretation, and revised the manuscript.
Sarah Ekeloef: This author collected the data, revised the analysis and interpretation, and revised the manuscript.
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Lau Thygesen: This author planned the study, refined the drafted protocol, planned the analysis, supervised and revised the analysis and interpretation, and revised the manuscript.
Ann Møller: This author planned the study, refined the drafted protocol, planned the analysis, supervised and revised the analysis and interpretation, and revised the manuscript.
Birgitte Brandstrup: This author planned the study, refined the drafted protocol, planned the analysis, supervised and revised the analysis and interpretation, revised the manuscript, and raised the funds.

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References

1. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet*. 2015;385(3):201-209F. doi:10.2471/BLT.15.159293
2. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005;242(3):326-341; discussion 341-3. doi:10.1097/01.sla.0000179621.33268.83
3. Tengberg LT, Cihoric M, Foss NB, et al. Complications after emergency laparotomy beyond the immediate postoperative period - a retrospective, observational cohort study of 1139 patients. *Anaesthesia*. 2017;72(3):309-316. doi:10.1111/anae.13721
4. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology*. 2005;103(1):25-32. doi:10.1177/153100350601800129
5. Abraham-Nordling M, Hjern F, Pollack J, Prytz M, Borg T, Kressner U. Randomized clinical trial of fluid restriction in colorectal surgery. *Br J Surg*. 2012;99(2):186-191. doi:10.1002/bjs.7702
6. Lobo DN, Bostock K a., Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: A randomised controlled trial. *Lancet*. 2002;359:1812-1818. doi:10.1016/S0140-6736(02)08711-1
7. Myles P, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy in major abdominal surgery (RELIEF): rationale and design for a multicentre randomised trial. *BMJ Open*. 2017;7(3):e015358. doi:10.1136/bmjopen-2016-015358
8. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238(5):641-648. doi:10.1097/01.sla.0000094387.50865.23
9. Feldheiser A, Aziz O, Baldini G, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: Consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand*. 2016;60(3):289-334. doi:10.1111/aas.12651
10. Ingraham AM, Cohen ME, Raval M V, Ko CY, Nathens AB. Comparison of hospital performance in emergency versus elective general surgery operations at 198 hospitals. *J Am Coll Surg*. 2011;212(1):20-28.e1. doi:10.1016/j.jamcollsurg.2010.09.026
11. Becher RD, Hoth JJ, Miller PR, Mowery NT, Chang MC, Meredith JW. A critical assessment of outcomes in emergency versus nonemergency general surgery using the American College of Surgeons National Surgical Quality Improvement Program database. *Am Surg*. 2011;77(7):951-959. http://www.ncbi.nlm.nih.gov/pubmed/21944366.
12. Becher RD, Hoth JJ, Miller PR, Meredith JW, Chang MC. Systemic inflammation worsens outcomes in emergency surgical patients. *J Trauma Acute Care Surg*. 2012;72(5):1140-1149. doi:10.1097/TA.0b013e3182516a97
13. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. *N Engl J Med*. 2001;345(19):1368-1377. doi:10.1056/NEJMoa010307
14. Mouncey PR, Osborn TM, Power GS, et al. Protocolised Management In Sepsis (ProMISe):A multicentre randomised controlled trial of the clinical effectiveness and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock. *Health Technol Assess (Rockv)*. 2015;19(97):1-150. doi:10.3310/hta19970
15. ProCESS Investigators, Yealy DM, Kellum JA, et al. A Randomized Trial of Protocol-Based Care for Early Septic Shock. *N Engl J Med*. 2014;370(18):1683-1693. doi:10.1056/NEJMoa1401602
16. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, et al. Goal-Directed Resuscitation for Patients with Early Septic Shock. *N Engl J Med*. 2014;371(16):1496-1506. doi:10.1056/NEJMoa1404380
17. Elm E von, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-808. doi:10.1136/bmj.39335.541782.AD
18. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7_suppl):22-25. doi:10.1177/1403494810387965
19. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. *JAMA Surg*. 2017;152(3):292. doi:10.1001/jamasurg.2016.4952

20. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae
21. Ford PNR, Thomas I, Cook TM, Whitley E, Peden CJ. Determinants of outcome in critically ill octogenarians after surgery: an observational study. *Br J Anaesth*. 2007;99(6):824-829. doi:10.1093/bja/aem307
22. Al-Temimi MH, Griffee M, Enniss TM, et al. When is death inevitable after emergency laparotomy? Analysis of the american college of surgeons national surgical quality improvement program database. *J Am Coll Surg*. 2012;215(4):503-511. doi:10.1016/j.jamcollsurg.2012.06.004
23. Harten J, Crozier JEM, McCreath B, et al. Effect of intraoperative fluid optimisation on renal function in patients undergoing emergency abdominal surgery: A randomised controlled pilot study (ISRCTN 11799696). *Int J Surg*. 2008;6(3):197-204. doi:10.1016/j.ijsu.2008.03.002
24. Pavlovic G, Diaper J, Ellenberger C, et al. Impact of early haemodynamic goal-directed therapy in patients undergoing emergency surgery: an open prospective, randomised trial. *J Clin Monit Comput*. 2016;30(1):87-99. doi:10.1007/s10877-015-9691-x
25. Bundgaard-Nielsen M, Secher NH, Kehlet H. "Liberal" vs. "restrictive" perioperative fluid therapy--a critical assessment of the evidence. *Acta Anaesthesiol Scand*. 2009;53(7):843-851. doi:10.1111/j.1399-6576.2009.02029.x
26. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. *Proc Nutr Soc*. 2010;69(4):488-498. doi:10.1017/S0029665110001734
27. MacKay G, Fearon K, McConnachie A, Serpell MG, Molloy RG, O'Dwyer PJ. Randomized clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. *Br J Surg*. 2006;93(12):1469-1474. doi:10.1002/bjs.5593
28. Kabon B, Akça O, Taguchi A, et al. Supplemental intravenous crystalloid administration does not reduce the risk of surgical wound infection. *Anesth Analg*. 2005;101(5):1546-1553. doi:10.1213/01.ANE.0000180217.57952.FE
29. Holte K, Foss NB, Andersen J, et al. Liberal or restrictive fluid administration in fast-track colonic surgery: a randomized, double-blind study. *Br J Anaesth*. 2007;99(4):500-508. doi:10.1093/bja/aem211
30. Kalyan JP, Rosbergen M, Pal N, et al. Randomized clinical trial of fluid and salt restriction compared with a controlled liberal regimen in elective gastrointestinal surgery. *Br J Surg*. 2013;100(13):1739-1746. doi:10.1002/bjs.9301
31. Shin CH, Long DR, McLean D, et al. Effects of Intraoperative Fluid Management on Postoperative Outcomes. *Ann Surg*. March 2017:1. doi:10.1097/SLA.0000000000002220
32. Vincent JL, Baron J-F, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA*. 2002;288(12):1499-1507. doi:10.1001/jama.288.12.1499
33. Abbott TEF, Pearse RM, Archbold RA, et al. A Prospective International Multicentre Cohort Study of Intraoperative Heart Rate and Systolic Blood Pressure and Myocardial Injury After Noncardiac Surgery. *Anesth Analg*. 2018;126(6):1936-1945. doi:10.1213/ANE.0000000000002560
34. Mouncey PR, Osborn TM, Power GS, et al. Trial of Early, Goal-Directed Resuscitation for Septic Shock. *N Engl J Med*. 2015;372(14):1301-1311. doi:10.1056/NEJMoa1500896
35. McLean DJ, Diaz-Gil D, Farhan HN, Ladha KS, Kurth T, Eikermann M. Dose-dependent Association between Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications. *Anesthesiology*. 2015;122(6):1201-1213. doi:10.1097/ALN.0000000000000674

Table 1. Baseline characteristics of the conservative or liberal fluid group of patients undergoing emergency gastrointestinal surgery

		Conservative group (peri-operative balance ≤2.5L), number of patients (%)	Liberal group (peri-operative balance >2.5L), number of patients (%)
Number of patients		179	163
Sex	Female	100 (55.9)	93 (57.1)
Age group	Years (median (IQR) φ)	70.0 [57.5, 79.0]	72.0 [66.0, 79.0]
Body mass index	Median (IQR)	23.9 [21.1, 26.8]	23.9 [21.5, 27.9]
	missing	14	10
Smoking habits	Current smoker	55 (32.4)	55 (34.2)
	missing	9	2
Alcohol intake, female / male	>7 / >14 units week^{-1}	15 (8.7)	24 (15.5)
	missing	7	8
ASA classification	1-2	110 (61.5)	77 (47.2)
	3-5	69 (38.5)	86 (52.8)
Sepsis-2 score, pre-operative	0-2	162 (91.5)	126 (77.8)
	3-4	15 (8.5)	36 (22.2)
	missing	2	1
Co-morbidity#	Heart disease	45 (25.1)	39 (23.9)
	Hypertension	73 (40.8)	79 (48.5)
	Pulmonary disease	26 (14.5)	31 (19.0)
	Liver disease	10 (5.6)	5 (3.1)
	Renal disease	11 (6.1)	15 (9.2)
	Diabetes mellitus	19 (10.6)	29 (17.8)
	Active cancer disease	24 (13.4)	30 (18.4)
Diagnosis	Adhesions	94 (52.5)	61 (37.4)
	Crohn disease	3 (1.7)	2 (1.2)
	Diverticulitis	13 (7.3)	15 (9.2)
	Hernia, strangulated	7 (3.9)	7 (4.3)
	Intraabdominal cancer	23 (12.8)	30 (18.4)
	Perforated ulcer	12 (6.7)	15 (9.2)
	Arterial ischemia	4 (2.2)	5 (3.1)
	Volvulus	11 (6.1)	9 (5.5)
	Other*	12 (6.7)	19 (11.7)
Surgical indication	Gastrointestinal obstruction	149 (83.2)	109 (66.9)
	Gastrointestinal perforation	30 (16.8)	54 (33.1)
Surgical procedure	Bowel resection	59 (33.0)	98 (60.1)
	Other procedure§	102 (57.0)	49 (30.1)
	Palliative surgeryθ	18 (10.1)	16 (9.8)
Laparoscopy		11 (6.1)	11 (6.7)
Primary anastomosis	Small bowel	16 (8.9)	21 (12.9)
	Ileo-colic	12 (6.7)	9 (5.5)
	Colo-colic	2 (1.1)	5 (3.1)
Time to surgery, hour			
From hospital admission	0-12 hours	67 (37.4)	71 (43.6)
	>12 hours	111 (62.0)	92 (56.4)
	missing	1	0
From assessment by surgeon	hour (median [IQR] φ)	3.0 [2.0, 6.0]	3.0 [2.0, 6.0]
	missing	1	0
Time of surgery, median [IQR]		1.6 [1.1, 2.3]	2.3 [1.6, 3.3]
		3	2
Time of anesthesia, median [IQR]		2.2 [1.8, 2.9]	3.0 [2.2, 4.0]
Immediate post-operative intensive care		15 (8.4)	53 (32.5)
Sepsis-2 score, post-operative	0-2	137 (76.5)	89 (54.6)
	3-4	38 (21.2)	72 (44.2)
	missing	4	2

#) Some patients have more than one co-morbidity. φ) Interquartile range. *) Unclassified surgery on the small or large bowel. §) Adhesiolysis, gastro-duodenorrhaphia, herniotomy, or peritoneal lavage. θ Exculpatory stoma formation or limited treatment.

Table 2. Peri-operative fluid administration, losses, and associated variables during and after emergency gastrointestinal surgery.

	Conservative group (peri-operative balance ≤2.5L), median [IQR] or no. (%) n = 179	Liberal group (peri-operative balance >2.5L), median [IQR] or no. (%) n = 163
Intra-operative data		
Fluid variables, mL		
iv[#] crystalloids	1400 [950, 1830]	2360 [1600, 3280]
iv colloids	0 [0, 0]	0 [0, 500]
iv glucose containing fluids	0 [0, 0]	0 [0, 0]
iv blood products	0 [0, 0]	0 [0, 0]
iv other fluids	110 [60, 170]	190 [90, 280]
Total iv fluid administration	1610 [1120, 2040]	2750 [2090, 3750]
Total iv fluid administration (mL kg^{-1} $hour^{-1}$)	9.8 [7.5, 12.7]	13.3 [9.0, 18.2]
missing, no.	3	0
Diuresis	120 [0, 380]	180 [70, 450]
Blood loss	0 [0, 130]	100 [0, 400]
Other loss	110 [70, 420]	120 [80, 260]
Total loss	490 [140, 1130]	600 [310, 1130]
Fluid balance	930 [570, 1290]	2030 [1550, 2790]
Hypotensive episodes	79 (44.1)	105 (64.4)
Vasopressor given	156 (87.2)	152 (93.3)
Ephedrine, mg, n = 118 / 100[§]	20.0 [10.0, 30.0]	17.5 [10.0, 30.0]
Norepinephrine, mg, n = 10 / 40[§]	1.5 [0.4, 3.4]	2.8 [1.8, 5.0]
Phenylephrine, mg, n = 94 / 112[§]	1.0 [0.4, 2.2]	2.8 [1.0, 5.7]
Post-operative data		
Fluid variables, mL		
iv crystalloids	720 [400, 1280]	1900 [1090, 3170]
iv colloids	0 [0, 0]	0 [0, 400]
iv glucose	0 [0, 0]	0 [0, 230]
iv blood products	0 [0, 0]	0 [0, 0]
iv other fluids	180 [5, 350]	410 [180, 1190]
Total iv fluid administration	950 [590, 1510]	2970 [1710, 5620]
Total iv fluid administration (mL kg^{-1} $hour^{-1}$)	3.5 [2.3, 4.8]	4.6 [3.7, 6.8]
missing, no.	3	1
Diuresis	140 [0, 500]	530 [110, 1320]
Blood loss	0 [0, 0]	0 [0, 0]
Other loss	140 [80, 280]	340 [140, 770]
Total loss	270 [110, 830]	970 [270, 2240]
Fluid balance	520 [250, 850]	1750 [1110, 3110]
Hypotensive episodes	17 (9.5)	46 (28.4)
missing, no.	0	1
Vasopressor given	22 (12.3)	71 (43.8)
Ephedrine, mg, n = 6 / 13[§]	15.0 [10.0, 20.0]	10.0 [10.0, 20.0]
Norepinephrine, mg, n = 12 / 47[§]	5.9 [3.4, 14.2]	12.8 [6.2, 20.0]
Phenylephrine, mg, n = 9 / 19[§]	2.2 [1.0, 8.1]	3.1 [0.5, 5.9]
Peri-operative fluid data		
Epidural analgesia, no. (%)	77 (43.0)	70 (42.9)
Total iv fluid administration	2610 [2160, 3310]	6000 [4290, 8930]
Total iv fluid administration (mL kg^{-1} $hour^{-1}$)	5.9 [4.1, 7.8]	7.3 [5.4, 10.2]
missing, no.	3	0
Total loss	920 [480, 2000]	1900 [960, 3350]
Fluid balance, mL	1580 [1000, 2040]	3620 [3020, 5340]
Fluid balance, mL kg^{-1} $hour^{-1}$	3.3 [1.7, 5.2]	4.7 [3.4, 7.2]
missing, no.	3	0

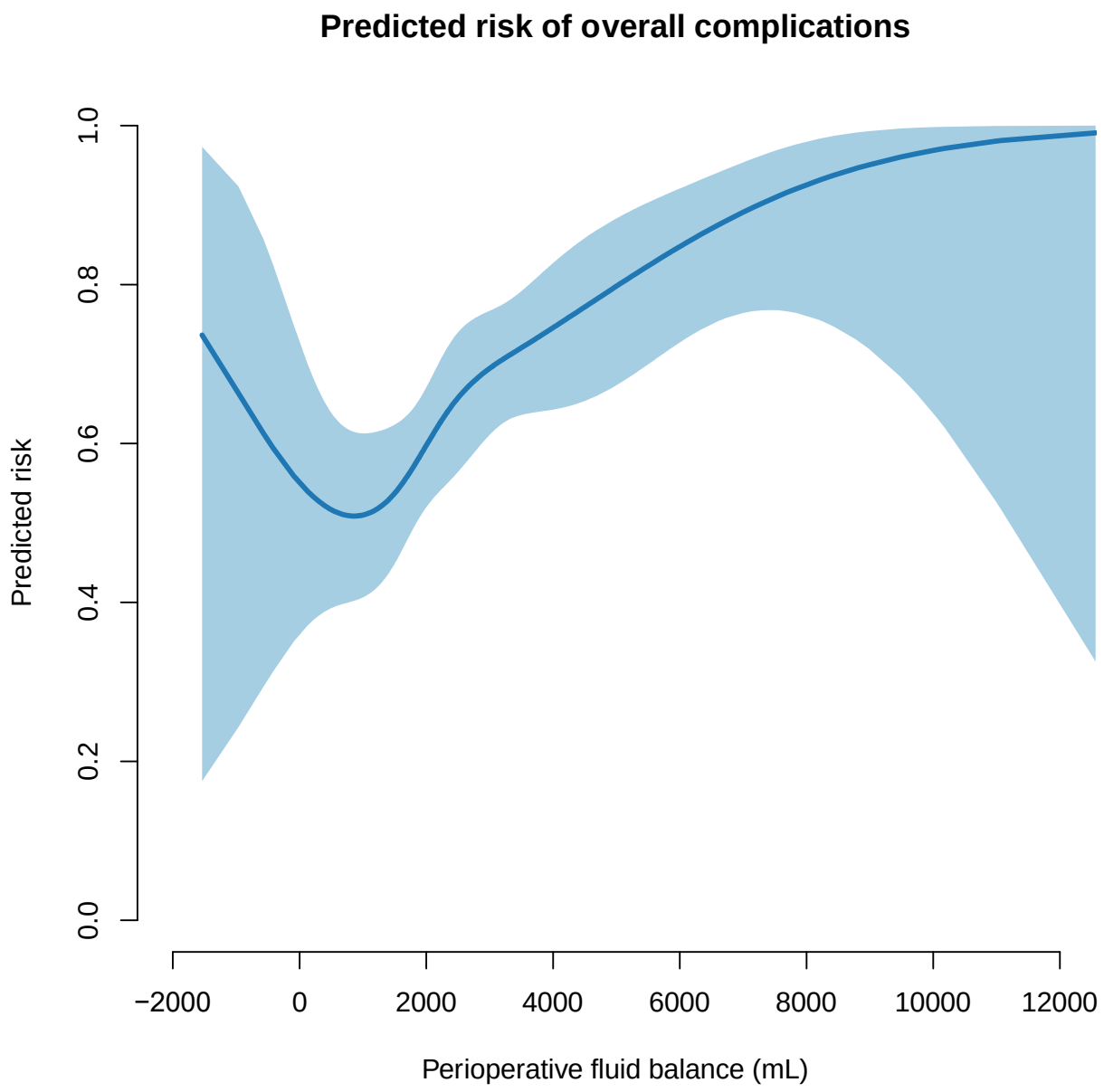
#) Intravenous. §) The result is presented for those who received vasopressor or inotropic as specified by the n = (conservative / liberal).

Table 3. Logistic regression analysis on the association between the peri-operative fluid balance and post-operative complications following emergency gastrointestinal surgery

Complication	Conservative group, N = 179 No. of patients (%)	Liberal group, N = 163 No. of patients (%)	Crude OR (95% CI) *	Crude p	Adjusted analysis¤ OR (95% CI) *	Adjusted analysis¤ p
			Any complication			
Primary outcome						
Overall complications	98 (58.0)	127 (73.4)	2.9 (1.8-4.7)	<0.001	2.6 (1.5-4.4)	<0.001
Subgroups of outcome						
Wound-related	39 (23.1)	48 (27.7)	1.5 (0.9-2.5)	0.105	1.6 (0.9-2.7)	0.123
Superficial wound rupture	18	25				
Rupture of the fascia	20	20				
Leakage of the anastomosis	1	3				
Cardiopulmonary	45 (26.6)	89 (51.4)	3.6 (2.3-5.7)	<0.001	3.2 (1.9-5.7)	<0.001
Arrhythmia	14	28				
Acute myocardial infarction	2	2				
Cardiac arrest	2	0				
Pleural effusion	9	17				
Pulmonary congestion	5	14				
Pulmonary edema	2	2				
Respiratory failure	11	26				
Renal	7 (4.1)	15 (8.7)	2.5 (1.0-6.7)	0.053	-	-
Need for dialysis	2	3				
Other renal§	5	12				
Infectious	73 (43.2)	90 (52.0)	1.8 (1.2-2.8)	0.008	1.6 (1.0-2.5)	0.071
Wound infection	14	12				
Pneumonia	35	65				
Urinary tract infection	18	11				
Other infections	6	2				
			Major complications			
Secondary outcome						
Major complication	46 (27.2)	65 (37.6)	1.9 (1.2-3.0)	0.005	1.6 (1.0-2.7)	0.077
Subgroups of outcome						
Wound-related	23 (13.6)	27 (15.6)	1.3 (0.7-2.5)	0.333	1.2 (0.6-2.4)	0.606
Superficial wound rupture	3	4				
Rupture of the fascia	19	20				
Leakage of the anastomosis	1	3				
Cardiopulmonary	22 (13.0)	45 (26.0)	2.7 (1.6-4.9)	0.000	2.5 (1.3-4.9)	0.006
Arrhythmia	1	3				
Acute myocardial infarction	4	2				
Cardiac arrest	2	2				
Pleural effusion	3	9				
Pulmonary congestion	0	0				
Pulmonary edema	2	4				
Respiratory failure	10	25				
Renal	5 (3.0)	12 (6.9)	2.8 (1.0-8.9)	0.061	-	-
Need for dialysis	2	3				
Other renal	3	9				
Infectious	14 (8.3)	15 (8.7)	1.2 (0.6-2.6)	0.647	1.1 (0.5-2.5)	0.874
Wound infection	10	3				
Pneumonia	4	12				
Urinary tract infection	0	0				
Other infections	0	0				
Death at post-operative day 90	36 (21.3)	51 (29.5)	1.8 (1.1-3.0)	0.019	1.3 (0.7-2.4)	0.477

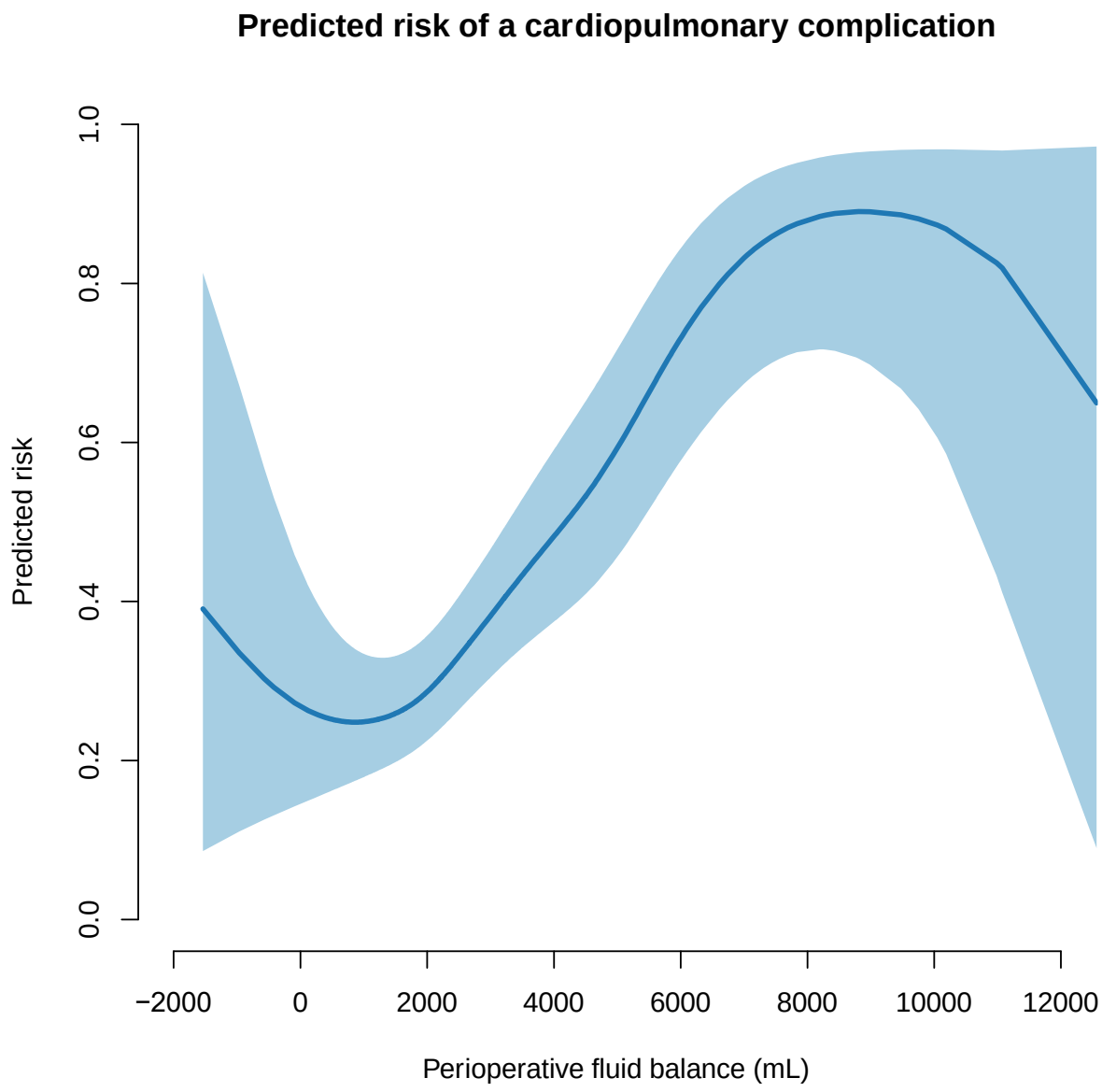
¤) Clinical risk factors adjusted for in the model: Sex, age in the potency, ASA class (dichotomized at ASA class 3), use of epidural analgesia (yes or no), use of vasopressors (yes or no), the type of surgery (bowel resection, palliative surgery, or other procedures), gastrointestinal obstruction or perforation, and the Hospital (Holbæk, Slagelse, or Køge). *) OR: Odds ratio, 95% CI: 95% confidence interval. §) Hydronephrosis with nephrostomy catheter or treatment stalled due to renal failure. A p-value <0.01 is considered significant.

Figure 1. The predicted risk of overall complications associated with the peri-operative fluid balance following emergency gastrointestinal surgery



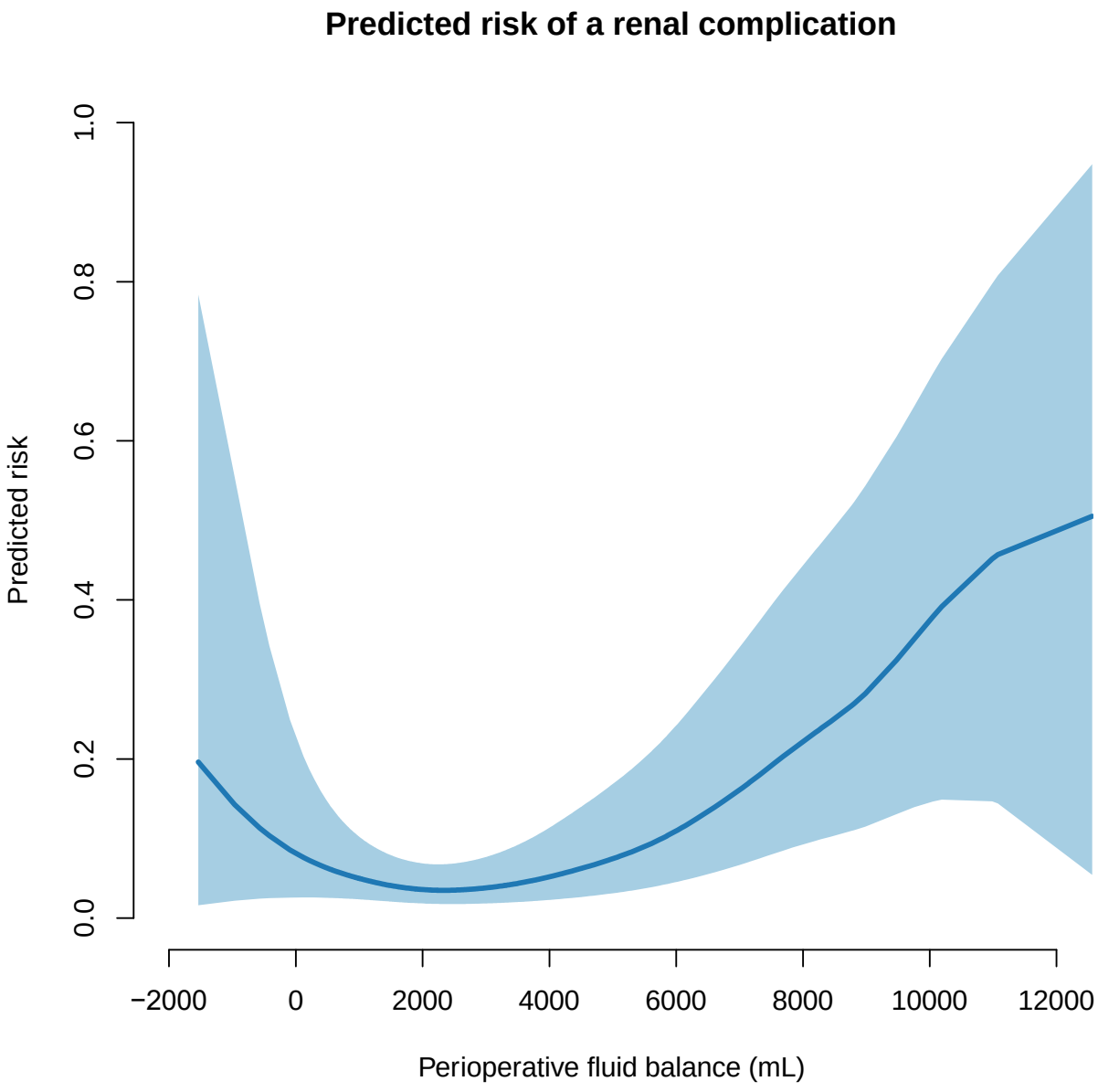
The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalized additive model with smoothing splines and four degrees of freedom. The parametric effect is p<0.001 and the non-parametric effect is p=0.572. The parametric calculation tests whether the fluid balance is linear associated with complications. The non-parametric analysis tests whether smoothing splines adds further precision to a linear relation of the model. A p-value <0.01 is considered significant.

Figure 2. The predicted risk of a cardiopulmonary complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalized additive model with smoothing splines and four degrees of freedom. The parametric effect is p<0.001 and the non-parametric effect is p=0.015. The parametric calculation tests whether the fluid balance is linear associated with complications. The non-parametric analysis tests whether smoothing splines adds further precision to a linear relation of the model. A p-value <0.01 is considered significant.

Figure 3. The predicted risk of a renal complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalized additive model with smoothing splines and four degrees of freedom. The parametric effect is p<0.001 and the non-parametric effect is p=0.080. The parametric calculation tests whether the fluid balance is linear associated with complications. The non-parametric analysis tests whether smoothing splines adds further precision to a linear relation of the model. A p-value <0.01 is considered significant.

Supplementary material

Title:

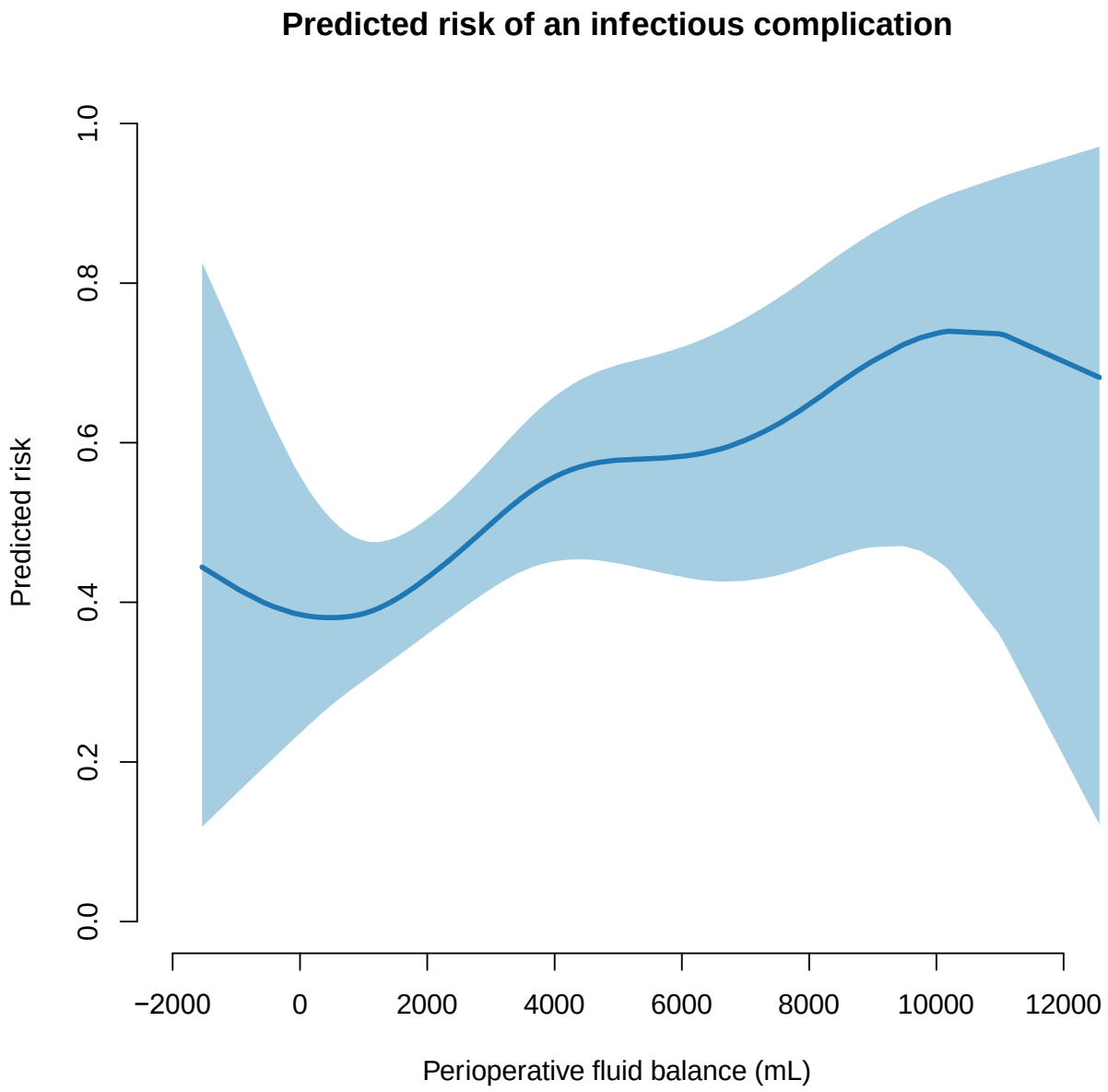
Peri-operative Fluid Administration and Complications in Emergency Gastrointestinal Surgery – an Observational Study

Authors:

Anders Winther Voldby, Anne Albers Aaen, Roberto Loprete, Hassan Ali Eskandarani, Anders Watt Boolsen, Simon Jønck, Sarah Ekeloef, Jakob Burcharth, Lau Caspar Thygesen, Ann Merete Møller, and Birgitte Brandstrup

Supplementary figure 1.

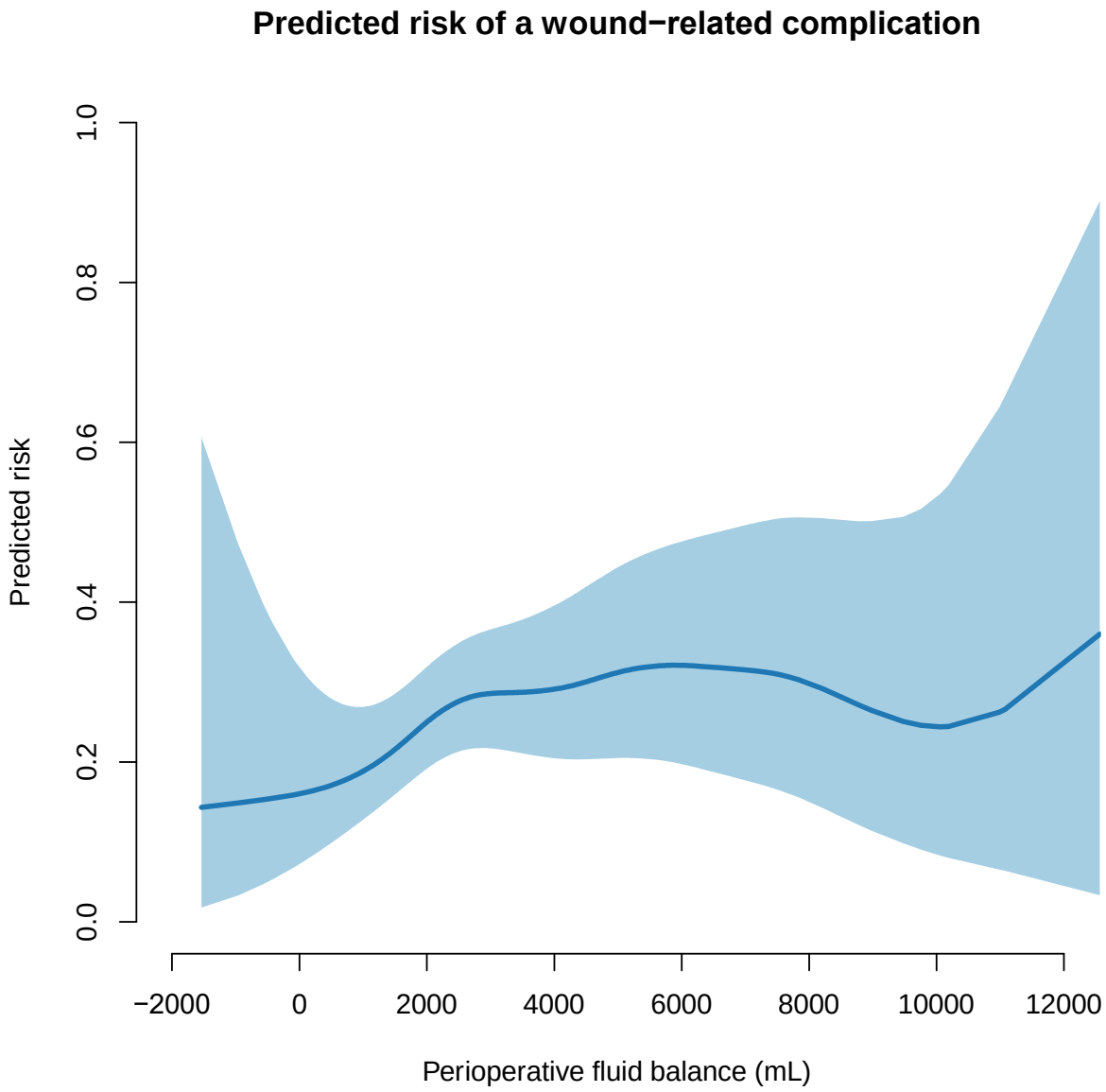
Predicted risk of an infectious complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect p=0.004. The non-parametric effect p=0.358. The parametric calculation tests whether the fluid balance is linear associated with complications. The non-parametric analysis tests whether smoothing splines adds further precision to a linear relation of the model. A p-value <0.01 is considered significant.

Supplementary figure 2.

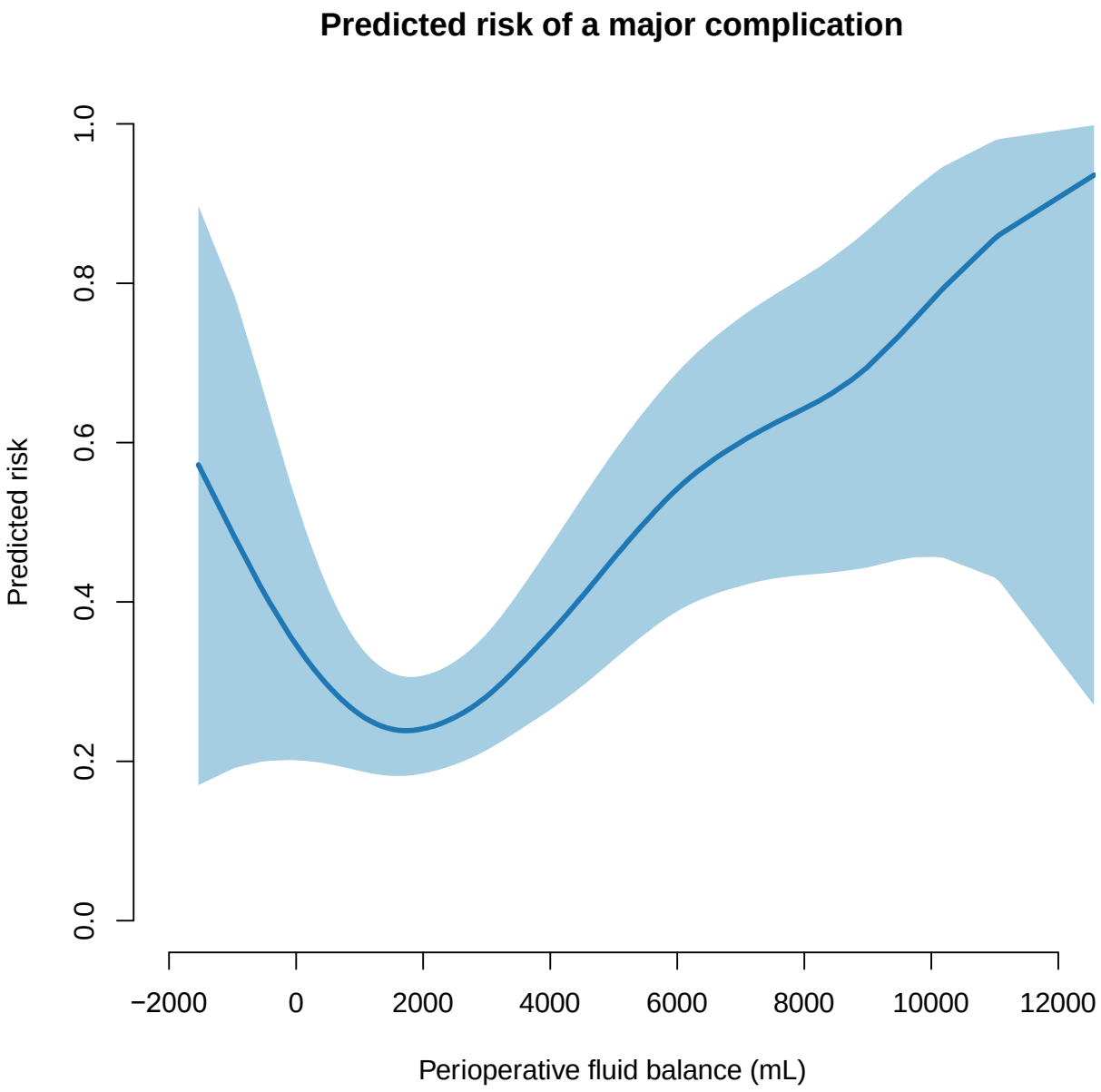
Predicted risk of a wound-related complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect p=0.182. The non-parametric effect p=0.187. The parametric calculation tests whether the fluid balance is linear associated with complications. The non-parametric analysis tests whether smoothing splines adds further precision to a linear relation of the model. A p-value <0.01 is considered significant.

Supplementary figure 3.

Predicted risk of a major complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect p<0.001. The non-parametric effect p=0.027. The parametric calculation tests whether the fluid balance is linear associated with complications. The non-parametric analysis tests whether smoothing splines adds further precision to a linear relation of the model. A p-value <0.01 is considered significant.

Supplementary Table 1.

Logistic regression analysis on the association between a peri-operative fluid balance and post-operative complications following emergency gastrointestinal surgery – only patients with a pre-operative sepsis-2 score of 0-2

	Conservative group (fluid balance ≤2.5L), n = 162	Liberal group (fluid balance >2.5L), n = 126	Crude		Adjusted analysis ¤	
	No. of patients (%)	No. of patients (%)	OR* (CI95%)	p	OR (CI95%)	p
Overall complications	86 (53)	96 (76)	2,8 (1,7-4,8)	<0,001	2,7 (1,5-4,8)	<0,001
Wound-related	36 (22)	42 (33)	1,8 (1,0-3,0)	0,036	1,8 (1,0-3,3)	0,058
Cardiopulmonary	36 (22)	60 (48)	3,2 (1,9-5,3)	<0,001	2,8 (1,5-5,3)	<0,001
Renal	5 (3)	9 (7)	2,4 (0,8-8,0)	0,122	-	-
Infectious	63 (39)	69 (55)	1,9 (1,2-3,1)	0,008	1,7 (1,0-2,8)	0,059

¤) Clinical risk factors adjusted for in the model: Sex, age in the potency, ASA class (dichotomised at ASA class 3), use of epidural analgesia (yes or no), use of vasopressors (yes or no), the type of surgery (bowel resection, palliative surgery or other procedures), gastrointestinal obstruction or perforation, and the Hospital (Holbæk, Slagelse, or Køge). *) OR: Odds ratio, 95% CI: 95% confidence interval. A p-value <0.01 is considered significant.

Supplementary table 2.

Logistic regression analysis on the association between the peri-operative fluid balance and post-operative complications following emergency gastrointestinal surgery – only patients not admitted to the intensive care unit immediately after surgery

	Conservative group (fluid balance ≤2.5L), n = 164	Liberal group (fluid balance >2.5L), n = 110	Crude		Adjusted analysis ¤	
	No. of patients (%)	No. of patients (%)	OR* (CI95%)	p	OR (CI95%)	p
Overall complications	86 (52)	80 (73)	2,4 (1,4-4,1)	<0,001	2,3 (1,3-4,1)	0,005
Wound-related	36 (22)	37 (34)	1,8 (1,0-3,1)	0,033	1,8 (1,0-3,4)	0,062
Cardiopulmonary	33 (20)	46 (42)	2,9 (1,7-4,9)	<0,001	3,0 (1,6-5,7)	<0,001
Renal	6 (4)	7 (6)	1,8 (0,6-5,7)	0,308	-	-
Infectious	63 (38)	58 (53)	1,8 (1,1-2,9)	0,020	1,7 (1,0-3,0)	0,058

¤) Clinical risk factors adjusted for in the model: Sex, age in the potency, ASA class (dichotomised at ASA class 3), use of epidural analgesia (yes or no), use of vasopressors (yes or no), the type of surgery (bowel resection, palliative surgery or other procedures), gastrointestinal obstruction or perforation, and the Hospital (Holbæk, Slagelse, or Køge). *) OR: Odds ratio, 95% CI: 95% confidence interval. A p-value <0.01 is considered significant.

8.2 Paper II

The Association of the Perioperative Fluid Balance and Cardiopulmonary Complications in Emergency Gastrointestinal Surgery – A Re-assessment of a Randomized Trial

Title:

The Association of the Perioperative Fluid Balance and Cardiopulmonary Complications in Emergency Gastrointestinal Surgery – A Re-assessment of a Randomized Trial

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Category of paper:

Original article, prospective cohort study based on data from the randomised clinical trial GAS-ART.
In manuscript.

Keywords:

Fluid therapy, intestinal obstruction, intestinal perforation, intraoperative care, postoperative complications, prospective study

Abstract

Background

The association between peri-operative fluid administration and risk of complications following emergency surgery is poorly studied. We tested the association between the peri-operative fluid balance and post-operative complications following emergency surgery for gastrointestinal obstruction or perforation.

Methods

We performed a planned re-assessment of data from the Goal-directed Fluid Therapy in Urgent Gastrointestinal Surgery Trial (GAS-ART) studying an intra-operative stroke volume optimisation and post-operative zero-balance fluid therapy versus a standard fluid therapy. The cohort was divided in three groups at a peri-operative fluid balance (FB) of 0.0L and 2.0L in a Low-FB, Moderate-FB, and High-FB group. We used a propensity adjusted logistic regression to analyse the association with cardiopulmonary complications. Further, the risk of complications was explored on a continuous scale of the fluid balance.

Results

We included 303 patients. In all, 44 patients belonged to the Low-FB group, 108 to the Moderate-FB group, and 151 to the High-FB group. The median [interquartile range] perioperative fluid balance was –0.9 L [–1.4, –0.6], 0.9 L [0.5, 1.3], and 3.8 L [2.7, 5.3]. The risk of cardiopulmonary complications was significantly higher in the High-FB group 3.4 (1.5-7.6), p=0.002 (odds ratio (95% confidence interval). On a continuous scale of the fluid balance the risk of cardiopulmonary complications was at a minimum at –1L to 1L.

Conclusion

A perioperative fluid balance above 2.0L was associated with an increased risk of cardiopulmonary complications following emergency surgery for gastrointestinal obstruction or perforation. Our findings imply that a perioperative fluid balance avoiding overload may improve the postoperative course.

Disclosure of Interest: None declared.

Introduction

Intravenous fluid administration is a vital part of the peri-operative care during emergency gastrointestinal surgery. However, the optimal fluid volume seems to follow a U-shaped curve with varying optimums depending on the complications studied.[1] A too rigid fluid administration may lead to hypovolemia, organ dysfunction, and even death.[2,3] In contrast, a too liberal fluid administration may lead to interstitial oedema, impaired wound healing, and cardiopulmonary complications which has been found in studies of elective surgical patients.[4–6] Based on these studies a zero-balance approach aiming at a stable body weight and fluid-balance is a part of the recommendations of Enhanced recovery after surgery (ERAS) during planned abdominal surgery.[7] Which fluid balance to aim for during emergency surgery is not known.

Patients having emergency surgery differ in several ways from patients undergoing planned surgery. They tend to be older, have more co-morbidities, and more than 40% of the patients have sepsis.[8] As such, ensuring a stable circulation while avoiding hypo- or hypervolemia, is a challenging obligation during emergency gastrointestinal surgery. Further, unknown pre-operative decline in food and fluid intake and pathological losses (e.g. blood or vomiting) oppose the application of a zero-balance approach during emergency surgery. Goal-directed fluid therapy (GDT) based on flow related markers possess the ability to prevent hypovolemic events while avoiding fluid overload. Several studies of planned surgical patients have tested GDT with an overall convincing effect.[9–11] However, studies evaluating the effect during emergency surgery are few.[12–14]

We recently presented the Goal-directed Fluid Therapy in Urgent Gastrointestinal Surgery Trial (GAS-ART); A multicentre randomised trial that enrolled 304 patients undergoing emergency gastrointestinal surgery and found no difference in major complications and death between an optimised GDT regimen (GDT-group) and a standard fluid regimen (STD-group).[14] A re-assessment of the data was planned to evaluate the influence of the peri-operative fluid balance on post-operative complications.

Resent evidence suggest that for patients undergoing emergency gastrointestinal surgery the risk of cardiopulmonary complications is at a minimum at a peri-operative fluid balance between 0.0 L and 2.0 L.[1] We re-analysed the GAS-ART data to test whether a peri-operative fluid administration aiming at a balance between 0.0 L and 2.0 L is related to a reduced risk of post-operative cardiopulmonnary complications following emergency gastrointestinal surgery.

Methods

The study was approved by the Ethical committee in Region Zealand (SJ-436) and all enrolled patients provided informed consent. The study was categorised as a drug study and registered at EudraCT (no. 2015-000563-14). The rational and design was published before study completion.[15]

We have recently published the main results.[14] In brief, we included patients scheduled for emergency surgery performed within hours, for radiologically verified gastrointestinal obstruction or perforation. Thus, minor surgical procedures were excluded (appendectomies, cholecystectomies) as well as gastrointestinal bleeding. The presence of a project anaesthetist to perform the intervention was mandatory. We excluded patients pregnant or younger than 18 years, having terminal illness (ASA class 5-6), receiving regular dialysis, with iatrogenic gastrointestinal perforation, unable to give informed consent, or having had intraabdominal surgery within 30 days. Patients were randomly assigned to the two fluid strategies in varying sized blocks by a computer-generated sequence and stratified by hospital and by gastrointestinal obstruction or perforation.

Pre-operative fluid administration was identical between the groups aiming at a heart rate below 100 min^{-1}, a systolic blood pressure above 100 mm Hg, and venous oxygen saturation above 95%. Intra-operatively the patients in the GDT-group were given boluses of human albumin 5% in saline based on a stroke-volume algorithm and a maintenance fluid administration ≤2 mL kg^{-1} $hour^{-1}$; after surgery the fluid administration aimed at a fluid-balance less than 2 L positive or body weight increase below 2 kg. Patients in the STD-group were intra-operatively given crystalloids to ensure a mean arterial pressure >65 mmHg and diuresis >0.5 mL kg^{-1} $hour^{-1}$. Vasopressors were administered to ensure a mean arterial pressure >65 mmHg in both groups in case the fluid regimen did not achieve that goal. For all patient haemoglobin was kept above 70 g L^{-1}, in patients with chronic ischemic heart disease above 80 g L^{-1}, or in case of acute ischemic heart disease above 90 g L^{-1}.

The intervention was continued until free per oral intake, discharge, or the seventh postoperative day in both groups. Additional aspects of the peri-operative care were based on local clinical practice and left to the discretion of the treating anaesthetises or surgeon. The GAS-ART trial found a lower intra-operative fluid administration in the GDT-group (1.5L vs. 2.0L) as expected per protocol. The post-operative fluid administration was comparable between the GDT- and the STD-group, indicating that a post-operative zero-balance strategy was standard of care at the study sites.

In this re-assessment the exposure variable was peri-operative fluid balance calculated as the difference between the fluid input and loss from induction of anaesthesia and until the end of post-operative day one (<48 hours post-operatively). We divided the cohort in three groups at a peri-operative balance of 0.0 L and 2.0 L in a 'Low-FB' (Fluid Balance), a ´Moderate-FB´, or a 'High-FB' group. The primary outcome was cardiopulmonary complications. The secondary outcomes were renal, wound-related, or infectious complications.

We collected all data prospectively in case rapport forms or from the patient file during the study period between August 2015 and August 2018. The fluid input included crystalloids, glucose containing fluids, colloids, packed blood products, platelets, fresh frozen plasma, intravenous administration of medicine, and oral administration of fluids. The fluid loss included diuresis, aspirate, ascites, drainage, stoma loss, perspiration, and blood loos. We ensured follow-up by clinical assessment during admission, and at 30 and 90 days by phone, registering the following complications: cardiopulmonary complications include pleural effusion, pulmonary congestion or oedema, respiratory failure requiring mechanical ventilation, arrhythmia, acute myocardial infarction, or cardiac arrest due to urgent cardiac disease; renal complications include acute kidney injury defined according to KDIGO guidelines (increase in plasma creatinine of more than 27 μmol L^{-1} or a 50% increase between a pre-operative creatinine value 30 day prior to surgery and a post-operative value within 48 hours), hydronephrosis with a need for catheter, or the need for renal replacement therapy; wound-related complications include superficial wound rupture or infection, deep wound infection, and fascia defect or rupture of the fascia; and infectious complications include superficial or deep wound infection, urinary tract infection, pneumonia, or intraabdominal abscess formation. We defined the complications before study initiation and data derived from the blinded assessment.[15]

Statistics

This is a secondary analysis of data from the GAS-ART trial. Parametric statistics was used for data following a gaussian distribution, otherwise non-parametric statistics was used. Number and percentages present categorical variables. The primary and secondary outcome was analysed by logistic regression. The Moderate-FB group served as reference. We used a weighted propensity score for each strata of the comparator. The variables included was chosen by the authors based on a priori knowledge of potential confounders. Continuous variables were age and body-mass-index. Categorical variables were: sex, ASA class (grouped in class 1-3 or 4-5), tobacco use (yes or no), excess alcohol intake (>7 units/week for women and >14 units/week for men), pre-operative sepsis-2-score (class 0-2 or 3-4), active cancer (yes or no),

cardiac co-morbidity (yes or no), pulmonary co-morbidity (yes or no), other co-morbidity including renal disease, liver disease or diabetes (yes or no), use of vasopressors (yes or no), the surgical method (laparotomy or laparoscopy), the type of surgery (resection of intestine with anastomosis or stoma formation, or no resection of intestine), the diagnosis (gastrointestinal obstruction, upper perforation (gastric, jejunal or ileac), or lower perforation (colonic or rectal)), and limited postoperative treatment (yes or no). We planned to adjust for hospital, but due to limited inclusion of patients at three hospitals this was not possible. In case of missing values of more than 5% multiple imputation was planned. We present the crude and adjusted results by odds ratio (OR) with a 95% confidence interval (95% CI). A two-tailed p-value of less than 0.05 was considered statistically significant. As supplementary to the above analysis, we presented the predicted risk of complications depending on the fluid balance on a continuous scale. A generalized additive model with smoothing splines and four degrees of freedom was used. The statistical plan was approved by the authors before commencing the analysing of data. The statistical software was R version 3.5.0 GUI 1.70 El Capitan ©R, 2016 and RStudio version 1.1.453.

Results

A total of 312 patients were randomised in the GAS-ART trial. Three patients withdrew their consent prior to surgery, and five patients did not have surgery. In this study we excluded one additional patient who withdrew consent the day after surgery, thus leaving 303 patients for analysis. Missing values were less than 5% in each covariate and multiple imputation was not used. The propensity score was stable for each comparator. No data were missing in the primary outcome. Regarding the renal complications, four patients (1%) had no pre-operative creatinine measure and five patients (2%) had no post-operative creatinine measure. File re-assessment showed an uneventful post-operative course for all nine patients, and they were included as event free (no renal complication) in the analysis.

The Low-FB group included 44 (14.5%) patients, the Moderate-FB group 108 (35.6%) patients, and the High-FB group 151 (49.8%) patients. The Low-FB group was only represented at Holbæk and Herlev hospital. The patients in the Low-FB group were younger, and had a higher incidence of liver disease or active cancer than patients in the two other groups (Table 1). Further, the majority of patients had adhesions and small bowel obstruction. In the High-FB group more patient had heart disease, small or large bowel perforation, or large bowel obstruction compared with the Moderate-FB or Low-FB group. Accordingly, more patients had a higher sepsis-2 score, a longer stay in the recovery room, or were transferred directly to the intensive care unit after surgery. The ASA score was comparable between the three groups. The majority of patients received intra-operative GDT in the Low-FB (59%) and Moderate-FB (57%) group in contrast to the High-FB group (41%).

During surgery the systolic and diastolic blood pressure, and the heart rate were comparable between the three groups (Table 2). However, events with a systolic blood pressure below 100 mmHg were more frequent in the Low-FB group, while events with a heart rate above 100 min^{-1} were more frequent in the High-FB group. Less patients were given intra-operative vasopressors in the Low-FB group (80%) compared with the Moderate-FB (87%) or High-FB group (87%). Further, the number of patients receiving norepinephrine increased with the fluid balance group. More patients were given vasopressors post-operatively in the High-FB group (9%).

The median [IQR] perioperative fluid balance was –0.9 L [–1.4, –0.6] in the Low-FB group, 0.9 L [0.5, 1.3] in the Moderate-FB group, and 3.8 L [2.7, 5.3] in the High-FB group. The median intra-operative fluid balance was approximately 0.5 L greater in the liberal group compared with the other groups, primarily due to a greater administration of crystalloids combined with an overall minor loss of fluids. Likewise, post-operatively the fluid balance was greater in the High-FB group due to a greater administration of crystalloids and glucose containing fluids combined with less diuresis. The post-operative negative fluid balance in the Low-FB group was mainly due to a greater diuresis.

Primary outcome

The overall risk of cardiopulmonary complications was 16.2% (49), of which 9% (4) were in the Low-FB group, 8% (9) in the Moderate-FB group, and 24% (36) in the High-FB group (Table 3). The difference was primarily due to a varying risk of pleural exudation, pulmonary congestion, or respiratory failure. The risk of cardiopulmonary complications was significantly increased in the High-FB group, OR 3.4 (1.5-7.6), p=0.002, but not in the in the Low-FB group, OR 1.7 (0.5-6.1), p=0.436. The predicted risk of cardiopulmonary complications was significantly associated with the peri-operative fluid balance on a continuous scale (Figure 1) and demonstrated a U-shaped relation. A peri-operative fluid balance approximating –1L to 1L was associated with the lowest risk of cardiopulmonary complications.

Secondary outcome

The overall risk of renal complications was 13.5% (41) with the greatest risk in the High-FB group. No significant association was found when comparing the fluid groups. However, the predicted risk of renal complications was significantly associated with the fluid balance on a continuous scale (Figure 2), and increased at a fluid balance above approximately 3 L.

The overall risk of infectious complications was 27.7% (84) and 13.9% (42) for wound-related complications. The risk of infectious or wound related complications were not associated with the fluid balance. The spline analysis confirmed this (Supplementary Figure 1 and 2).

Discussion

In this prospective trial of patients undergoing emergency surgery for gastrointestinal obstruction or perforation, we found that the risk of cardiopulmonary complications was significantly associated with a peri-operative fluid balance above 2.0 L compared with a fluid balance between 0.0L and 2.0 L. Patients with a peri-operative fluid balance above 2 L had more often heart disease, gastrointestinal perforation, or a higher pre-operative sepsis-2 score. We found that a fluid balance below 0.0 L was not associated with an increased risk of any complications. Patients in this group were more often known with active cancer or liver disease, and had more often obstructive bowel disease.

The increased risk of cardiopulmonary complications in the High-FB group support our hypothesis that a perioperative fluid balance above 2 L is associated with an increased risk of complications following emergency gastrointestinal surgery.[1] Our results align with findings in studies of patients undergoing elective abdominal surgery, which demonstrate a reduced risk of overall or cardiopulmonary complications from a more restrictive intra-operative fluid administration (1.4 L to 3.1 L) compared with a liberal fluid administration (3.9 L to 5.8 L).[4–6] In contrast, two studies found no significant difference in complications between a restrictive (1.6 L to 1.9 L) or liberal fluid group (3.3 L to 5.1L).[16,17] Noteworthy, a post-operative negative body weight was reported the days after surgery in these studies. The largest study to date found a non-significant reduction of pulmonary oedema in the restrictive vs liberal group (1.4% vs 2.2%, p=0.10).[3] The fluid balance was 1.4 L vs. 3.1 L and comparable with the Moderate-FB (0.9 L) and High-FB group (3.8 L) in our study. All-together, it seems that a liberal peri-operative fluid balance is associated with an increased risk of cardiopulmonary complications following elective as well as emergency gastrointestinal surgery.

We found no association between a low fluid balance and cardiopulmonary complications, which does not support our proposition of an adverse outcome from a negative fluid balance. A negative fluid balance may associate with more hypovolemic events and organ damage. However, GDT algorithms may encompass the ability to prevent hypovolemic events. A pilot study and an early terminated study have tested the effect of GDT during emergency surgery and found no increased risk of complications in the group receiving the lowest fluid administration combined with GDT optimisation.[12,13] In similarity, the GAS-ART trial found no difference in the risk of complications.[14] In addition to the intra-operative care accommodating hypovolemic events, all three studies document a post-operative positive fluid balance in the allocated groups, which indicate a judicious post-operative care. We found the predicted risk of cardiopulmonary complications to be minimal at a peri-operative fluid balance as low as -1L to 1L (Figure 1). It is likely that the thorough protocolised post-operative care for up to a week after surgery in the GAS-ART trial, may

have preserved organ function despite an overall peri-operative fluid strategy approximating a zero-balance principle in emergency surgery.

The goal-directed fluid regimen in the GAS-ART trial attempted to prevent hypovolemic events while avoiding fluid overload. Futier and colleagues compared a restrictive GDT-regimen versus a liberal GDT-regimen in elective abdominal surgery. They found more patients with anastomotic leakage, sepsis, or acute lung injury in the restrictive regimen which was argued to be due to more hypovolemic episodes.[18] In contrast, Lobo and colleagues found significantly fewer complications with less cardiovascular and tissue healing events from a restrictive GDT regimen compared to a liberal GDT regimen.[19] They argued that a greater administration of colloid boluses in the restrictive group reduced the risk of hypovolemic events and thereby the adverse events. In our study the administration of albumin was lesser in the Low-FB group indicating fewer patients with hypovolemic events. Conversely the administration of albumin was the highest in the High-FB group, as were the number of patients receiving vasopressors, suggesting more hypovolemic events. The results may partly explain the increased risk of cardiopulmonary events in the high-FB group as suggested by Futier. However, the risk of cardiopulmonary complications continued to increase with an increase of the fluid balance (Figure 1) suggesting a benefit from a more restrictive fluid approach supporting the findings by Lobo and colleagues.

Of the secondary outcomes, only renal complications were significantly associated with the fluid balance on a continuous scale. The risk of renal complications increased when the fluid balance passed approximately 3L (Figure 2). A positive fluid balance has previously been associated with acute renal failure.[20] In contrast, Myles and colleagues found a greater risk of acute kidney injury and a need for renal-replacement therapy in the group receiving a restrictive fluid regimen compared with a liberal regimen in high-risk mixed surgical patients (peri-operative fluid balance 1.4 L vs. 3.1 L).[3] Importantly, in the restrictive group no protocolised action existed for the treatment of oliguria or anuria at the post-operative care unit or on the wards. In comparison, two studies with a clear post-operative treatment plan for oliguria found no increased risk of renal complications from a restrictive fluid regimen (2.6 L to 2.7 L) compared with liberal regimen (5.0 L to 5.4 L).[4,21] A resent observational study of non-cardiac procedures found a restrictive as well as a liberal fluid administration to be associated with increased risk of renal complications,[22] and an intra-operative fluid administration between 1.8 L to 2.7 L to have the lowest risk of acute kidney injury. These findings are in agreement with the findings of an observational study of emergency gastrointestinal procedures: a fluid balance between 1.5 L to 3.5 L was associated with the lowest risk of renal complication.[1] It seems that a positive fluid balance favours renal function, yet, a too liberal fluid administration may be harmful as well.

A meta-analysis found no association between restrictive fluid regimens and post-operative oliguria or acute renal failure.[23] Importantly, the study did not address the post-operative fluid administration in the studies and the duration of oliguria has been shown to associate with acute kidney injury.[24] In contrast, two observational studies found that intra-operative oliguria is associated with acute kidney injury.[24,25] However, the positive predictive value of the association between intra-operative oliguria and acute kidney injury is poor, while the absence of oliguria has a high predictive value of a post-operative course without acute kidney injury.[26] Our results support the latter findings even in case of a negative peri-operative fluid balance as observed in the Low-FB group. We found no increased risk of acute kidney injury in the Low-FB group despite the negative fluid balance. Noteworthy, the intra- and post-operative diuresis were highest in the Low-FB group, indicating an acceptable renal function.[26] Conversely, diuresis was the lowest in the High-FB group despite a more positive fluid balance, which might have counteracted an impaired renal function.

Implication of study findings

Our findings show that fluid overload in patients undergoing emergency gastrointestinal surgery is related to an increased risk of cardiopulmonary complications. A zero-balance (–1 L to 1 L) fluid strategy was associated with the lowest predicted risk of cardiopulmonary complications. However, the risk of renal complications sims to favour from a higher fluid balance of up to 3L. Future randomised clinical trials are encouraged to focus on the segment of patients continuously receiving more fluid than they lose after surgery or protocols avoiding persistent fluid accumulation during and after surgery. Future trials are encouraged to consider that different post-operative complications may benefit unevenly from different fluid balances.

The strengths of our study is that the data were prospectively collected from multiple centres in a randomised setup with an intra- and post-operative protocolised fluid administration, and clearly predefined outcomes. The intervention and data collection were monitored and the outcome assessed blinded. Moreover, we performed a propensity score adjustment of the logistic regression analysis in order to correct for several confounders. Our study also has limitations. Some variables differed between the fluid groups and the result is prone to known as well as unknown confounders. We did not collect data on drug administration. Further, it was not possible to adjust for the hospitals in this analysis, due to zero patients in the Low-FB-group at some sites. The fluid balance was based on intra- and post-operative fluid data up to 48 hours after surgery only. Fluid administration and loss outside this period may have

influenced the outcome. We did not include the data following that period partly because the fluid registration was ceased due to oral intake or discharge. However, the time span for the registered fluid data is in alignment with most other studies in the field.

In conclusion, a perioperative fluid balance above 2.0 L was associated with an increased risk of cardio-pulmonary complications following emergency surgery for gastrointestinal obstruction or perforation. We found no association between a negative fluid balance and cardiopulmonary complications. The risk of cardiopulmonary complications was at a minimum at a peri-operative fluid balance of –1 L to 1 L. The risk of renal complications was significantly associated with a peri-operative fluid balance exceeding 3 L. No association was found between the peri-operative fluid balance and wound-related or infectious complications. Our findings imply that aiming at a peri-operative zero-balance fluid strategy (balance <2 L) may reduce the risk of post-operative cardiopulmonary complications following emergency gastrointestinal surgery.

References

1. Voldby AW, Aaen AA, Loprete R, et al. Peri-operative Fluid Administration and Complications in Emergency Gastrointestinal Surgery – an Observational Study. *2020.*:1-26.
2. Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost. *Intensive Care Med*. 1994;20(2):99-104. http://www.ncbi.nlm.nih.gov/pubmed/8201106. Accessed February 17, 2019.
3. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. *N Engl J Med*. 2018;378(24):NEJMoa1801601. doi:10.1056/NEJMoa1801601
4. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238(5):641-648. doi:10.1097/01.sla.0000094387.50865.23
5. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology*. 2005;103(1):25-32. doi:10.1177/153100350601800129
6. Abraham-Nordling M, Hjern F, Pollack J, Prytz M, Borg T, Kressner U. Randomized clinical trial of fluid restriction in colorectal surgery. *Br J Surg*. 2012;99(2):186-191. doi:10.1002/bjs.7702
7. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. *JAMA Surg*. 2017;152(3):292. doi:10.1001/jamasurg.2016.4952
8. Becher RD, Hoth JJ, Miller PR, Mowery NT, Chang MC, Meredith JW. A critical assessment of outcomes in emergency versus nonemergency general surgery using the American College of Surgeons National Surgical Quality Improvement Program database. *Am Surg*. 2011;77(7):951-959. http://www.ncbi.nlm.nih.gov/pubmed/21944366.
9. Scheeren TWL, Wiesenack C, Gerlach H, Marx G. Goal-directed intraoperative fluid therapy guided by stroke volume and its variation in high-risk surgical patients: A prospective randomized multicentre study. *J Clin Monit Comput*. 2013;27:225-233. doi:10.1007/s10877-013-9461-6
10. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg*. 2006;93(9):1069-1076. doi:10.1002/bjs.5454
11. Mayer J, Boldt J, Mengistu AM, Röhm KD, Suttner S. Goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized, controlled trial. *Crit Care*. 2010;14(1):R18. doi:10.1186/cc8875
12. Harten J, Crozier JEM, McCreath B, et al. Effect of intraoperative fluid optimisation on renal function in patients undergoing emergency abdominal surgery: A randomised controlled pilot study (ISRCTN 11799696). *Int J Surg*. 2008;6(3):197-204. doi:10.1016/j.ijsu.2008.03.002
13. Pavlovic G, Diaper J, Ellenberger C, et al. Impact of early haemodynamic goal-directed therapy in patients undergoing emergency surgery: an open prospective, randomised trial. *J Clin Monit Comput*. 2016;30(1):87-99. doi:10.1007/s10877-015-9691-x
14. Aaen AA, Voldby AW, Storm N, et al. Goal Directed Fluid Therapy in Urgent Abdominal Surgery – Results from a Rndomized Clinical Multicentre Trial. The GAS-ART Trial. *Manuscr*. 2020.
15. Voldby AW, Aaen AA, Møller AM, Brandstrup B. Goal-directed fluid therapy in urgent GAstrointestinal Surgery—study protocol for A Randomised multicentre Trial: The GAS-ART trial. *BMJ Open*. 2018;8(11):e022651. doi:10.1136/bmjopen-2018-022651
16. Kalyan JP, Rosbergen M, Pal N, et al. Randomized clinical trial of fluid and salt restriction compared with a controlled

liberal regimen in elective gastrointestinal surgery. *Br J Surg*. 2013;100(13):1739-1746. doi:10.1002/bjs.9301

17. Holte K, Foss NB, Andersen J, et al. Liberal or restrictive fluid administration in fast-track colonic surgery: a randomized, double-blind study. *Br J Anaesth*. 2007;99(4):500-508. doi:10.1093/bja/aem211
18. Futier E, Constantin J-M, Petit A, et al. Conservative vs restrictive individualized goal-directed fluid replacement strategy in major abdominal surgery: A prospective randomized trial. *Arch Surg*. 2010;145(12):1193-1200. doi:10.1001/archsurg.2010.275
19. Lobo SM, Ronchi LS, Oliveira NE, et al. Restrictive strategy of intraoperative fluid maintenance during optimization of oxygen delivery decreases major complications after high-risk surgery. *Crit Care*. 2011;15(5):R226. doi:10.1186/cc10466
20. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care*. 2008;12(3):1-7. doi:10.1186/cc6916
21. Hübner M, Schäfer M, Demartines N, et al. Impact of restrictive intravenous fluid replacement and combined epidural analgesia on perioperative volume balance and renal function within a Fast Track program. *J Surg Res*. 2012;173(1):68-74. doi:10.1016/j.jss.2010.08.051
22. Shin CH, Long DR, McLean D, et al. Effects of Intraoperative Fluid Management on Postoperative Outcomes. *Ann Surg*. March 2017:1. doi:10.1097/SLA.0000000000002220
23. Egal M, de Geus HRH, van Bommel J, Groeneveld ABJ. Targeting oliguria reversal in perioperative restrictive fluid management does not influence the occurrence of renal dysfunction. *Eur J Anaesthesiol*. 2016;33(6):425-435. doi:10.1097/EJA.0000000000000416
24. Shiba A, Uchino S, Fujii T, Takinami M, Uezono S. Association between intraoperative oliguria and acute kidney injury after major noncardiac surgery. *Anesth Analg*. 2018;127(5):1229-1235. doi:10.1213/ANE.0000000000003576
25. Mizota T, Yamamoto Y, Hamada M, Matsukawa S, Shimizu S, Kai S. Intraoperative oliguria predicts acute kidney injury after major abdominal surgery. *Br J Anaesth*. 2017;119(6):1127-1134. doi:10.1093/bja/aex255
26. Myles PS, McIlroy DR, Bellomo R, Wallace S. Importance of intraoperative oliguria during major abdominal surgery: findings of the Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery trial. *Br J Anaesth*. 2019;122(6):726-733. doi:10.1016/j.bja.2019.01.010

Table 1. Background data according to the fluid balance of patients undergoing emergency gastrointestinal surgery.

	Low-FB§ group, fluid balance <0.0L n = 44	Moderate-FB group, fluid balance 0.0-2.0L n = 108	High-FB group, fluid balance >2.0L n = 151
Sex, female, No (%)	24 (54.5)	55 (50.9)	89 (58.9)
Age, years, Median [IQR]	66.0 [56.8, 71.2]	69.0 [57.0, 78.0]	72.0 [61.0, 81.0]
Hospital, No (%)			
Holbaek	5 (11.4)	19 (17.6)	43 (28.5)
Svendborg	0 (0.0)	0 (0.0)	7 (4.6)
Slagelse	0 (0.0)	4 (3.7)	12 (7.9)
Odense	0 (0.0)	9 (8.3)	7 (4.6)
Herlev	39 (88.6)	76 (70.4)	82 (54.3)
Body mass index, Median [IQR]	24.8 [20.6, 29.3]	24.3 [22.0, 27.4]	24.1 [21.5, 26.2]
missing	3	6	17
Actively smoking, No (%)	8 (18.2)	23 (21.3)	40 (26.5)
Excess alcohol intake* No (%)	5 (11.4)	12 (11.1)	18 (11.9)
ASA classification, No (%)			
1-2	26 (59.1)	70 (64.8)	88 (58.3)
3-4	18 (40.9)	38 (35.2)	63 (41.7)
Sepsis-2 score, No (%)			
0-2	43 (97.7)	107 (99.1)	135 (89.4)
3-4	1 (2.3)	1 (0.9)	16 (10.6)
Co-morbidity, No (%)			
Heart disease	6 (13.6)	23 (21.3)	42 (27.8)
Hypertension	16 (36.4)	44 (40.7)	57 (37.7)
Pulmonary disease	10 (22.7)	15 (13.9)	28 (18.5)
Renal disease	5 (11.4)	11 (10.2)	13 (8.6)
Liver disease	4 (9.1)	3 (2.8)	2 (1.3)
Diabetes mellitus	4 (9.1)	15 (13.9)	14 (9.3)
Active cancer	10 (22.7)	16 (14.8)	14 (9.3)
Randomisation, GDT-group, No (%)	26 (59.1)	62 (57.4)	62 (41.1)
Intraabdominal pathology, No (%)			
Ulcer disease	2 (4.5)	7 (6.5)	17 (11.3)
Small bowel perforation	0 (0.0)	3 (2.8)	8 (5.3)
Large bowel perforation	3 (6.8)	9 (8.3)	19 (12.6)
Small bowel obstruction	37 (84.1)	74 (68.5)	85 (56.3)
Large bowel obstruction	2 (4.5)	10 (9.3)	17 (11.3)
Necrosis of intestine	0 (0.0)	2 (1.9)	1 (0.7)
Otherθ	0 (0.0)	3 (2.8)	4 (2.6)
Surgical procedure, No (%)			
Gastro- or duodenoraphia	2 (4.5)	6 (5.6)	17 (11.3)
Adhesiolysis	27 (61.4)	44 (40.7)	49 (32.5)
Resection of small intestine	2 (4.5)	20 (18.5)	29 (19.2)
Resection of large intestine	7 (15.9)	17 (15.7)	28 (18.5)
Other#	6 (13.6)	21 (19.4)	28 (18.5)
Resection of intestine or stoma formation, No (%)	17 (38.6)	46 (42.6)	69 (45.7)
Anastomosis			
Small bowel	3 (6.8)	18 (16.7)	30 (19.9)
Ileo-colic	4 (9.1)	12 (11.1)	8 (5.3)
Colo-colic	0 (0.0)	0 (0.0)	2 (1.3)
Laparoscopy, No (%)	7 (15.9)	26 (24.1)	33 (21.9)
Time of anaesthesia, hours, Median [IQR]	2.4 [1.8, 3.1]	2.4 [1.6, 3.5]	2.5 [1.9, 3.4]
Time in recovery room, hours, Median [IQR]	3.6 [2.7, 6.1]	4.2 [2.8, 6.0]	5.8 [2.8, 12.7]
missing	2	2	16
Postoperative ICU care, immediately, No (%)	2 (4.5)	5 (4.6)	24 (15.9)
Limited treatment postsurgical, No (%)	3 (6.8)	2 (1.9)	7 (4.6)

§ Fluid Balance. * >7 / 14 units week^{-1}; women / men. θ Intraluminal obstruction of intestine, perforated appendicitis. # Drainage, hernia repair, enterotomy, or stoma formation.

Table 2. Perioperative fluid administration, losses, and associated variables during emergency gastrointestinal surgery divided according to fluid group.

	Low-FB§ group (fluid balance <0.0L) n = 44	Moderate-FB group (fluid balance 0.0-2.0L) n = 108	High-FB group (fluid balance >2.0L) n = 151
Intra-operative			
Blood pressure (BP) and heart rate (HR)			
Systolic BP at 1 hour, mm Hg	100 [92, 113]	108 [95, 120]	103 [92, 120]
Diastolic BP at 1 hour, mm Hg	52 [49, 58]	55 [48, 61]	54 [47, 60]
HR at 1 hour, min^{-1}	73 [65, 81]	77 [69, 86]	84 [71, 94]
Systolic BP < 100 mm Hg, no.	42 (95.5)	99 (91.7)	135 (89.4)
HR > 100 min^{-1}, no.	6 (13.6)	25 (23.1)	55 (36.4)
Fluid variables, mL			
Iv* crystalloids	730 [300, 1160]	680 [400, 1010]	1000 [600, 1730]
iv colloids	250 [250, 510]	300 [0, 550]	390 [0, 710]
Other	420 [200, 570]	360 [200, 500]	390 [160, 520]
Total iv fluid administration	1680 [1180, 2160]	1440 [1110, 1960]	2030 [1450, 2700]
Diuresis	260 [100, 500]	150 [40, 270]	180 [60, 300]
Blood loss	0 [0, 200]	0 [0, 100]	0 [0, 50]
Other loss	0 [0, 260]	0 [0, 400]	0 [0, 160]
Total loss	570 [280, 800]	450 [190, 820]	360 [150, 800]
Fluid balance	970 [480, 1430]	910 [640, 1320]	1480 [1000, 2120]
Vasopressor given, patients (%)	35 (79.5)	94 (87.0)	132 (87.4)
Ephedrine, patients (%)	26 (59.1)	71 (65.7)	85 (56.3)
Dose, mg	25.0 [20.0, 33.8]	20.0 [10.0, 30.0]	20.0 [10.0, 40.0]
Phenylephrine, patients (%)	4 (9.1)	60 (55.6)	102 (67.5)
Dose, mg	0.5 [0.2, 0.8]	0.6 [0.4, 1.2]	0.8 [0.4, 1.4]
Norepinephrine, patients (%)	4 (9.1)	14 (13.0)	41 (27.2)
Dose, mg	0.6 [0.2, 1.2]	0.2 [0.1, 3.5]	0.3 [0.1, 0.9]
Post-operative			
Fluid variables, mL			
iv crystalloids	820 [200, 1200]	1010 [500, 2000]	2220 [1100, 3300]
iv colloids	0 [0, 0]	0 [0, 0]	0 [0, 250]
Glucose containing fluids	0 [0, 1000]	0 [0, 1000]	1000 [0, 1680]
Other	1170 [350, 2080]	1330 [570, 2100]	2200 [1420, 3250]
Total iv fluid administration	2460 [1760, 3800]	3140 [2200, 4420]	5430 [4260, 7430]
Diuresis	2250 [1670, 3420]	1720 [910, 2750]	1470 [1030, 2400]
Other loss	1690 [1250, 3560]	1290 [940, 1990]	1340 [960, 2000]
Total loss	5040 [3830, 6170]	3460 [2110, 4420]	3100 [2260, 4340]
Fluid balance	-1960 [-2450, -1540]	80 [-550, 480]	2170 [1320, 3410]
Vasopressor given, patients	2 (4.5)	4 (3.7)	14 (9.3)
Peri-operative			
Total fluid administration, mL	4380 [3250, 5540]	4880 [3500, 6230]	7820 [6120, 9800]
Total fluid loss, mL	5700 [4110, 7690]	4000 [2480, 5170]	3640 [2620, 5080]
Fluid balance, mL	-870 [-1440, -550]	930 [540, 1330]	3760 [2730, 5290]

§ Fluid Balance. * intravenous.

Table 3. Risk of complications associated with the perioperative fluid group following emergency gastrointestinal surgery.

	Low-FB§ group (fluid balance <0.0L) n = 44	Moderate-FB group (fluid balance 0.0-2.0L) n = 108	High-FB group (fluid balance >2.0L) n = 151
Cardio-pulmonary complications	4 (9.1)	9 (8.3)	36 (23.8)
Arrhythmia, atrial	2 (4.5)	4 (3.7)	6 (4.0)
Arrhythmia, ventricular	1 (2.3)	0 (0.0)	1 (0.7)
Acute myocardial infarction	0 (0.0)	1 (0.9)	2 (1.3)
Cardiac arrest	0 (0.0)	0 (0.0)	1 (0.7)
Pleural exudation	1 (2.3)	0 (0.0)	9 (6.0)
Pulmonary congestion	0 (0.0)	2 (1.9)	10 (6.6)
Respiratory failure	0 (0.0)	2 (1.9)	7 (4.6)
Renal complications	5 (11.4)	11 (10.2)	25 (16.6)
Acute Kidney Injury*	5 (11.4)	10 (9.3)	18 (11.9)
Hydronephrosis	0 (0.0)	1 (0.9)	2 (1.3)
Renal failure demanding dialysis	0 (0.0)	0 (0.0)	5 (3.3)
Infectious complications	10 (22.7)	29 (26.9)	45 (29.8)
Superficial wound infection	2 (4.5)	4 (3.7)	8 (5.3)
Deep wound infection	1 (2.3)	3 (2.8)	1 (0.7)
Urinary tract infection	2 (4.5)	4 (3.7)	14 (9.3)
Pneumonia	5 (11.4)	14 (13.0)	21 (13.9)
Intraabdominal abscess	0 (0.0)	4 (3.7)	1 (0.7)
Wound related complications	6 (13.6)	19 (17.6)	17 (11.3)
Superficial wound rupture	3 (6.8)	9 (8.3)	5 (3.3)
Superficial wound infection	2 (4.5)	2 (1.9)	5 (3.3)
Deep wound infection	1 (2.3)	1 (0.9)	1 (0.7)
Fascia rupture	0 (0.0)	7 (6.5)	6 (4.0)

The results present number of patients with complications. Only the first appearing complication is presented for the sub-variables of the four groups of complications.

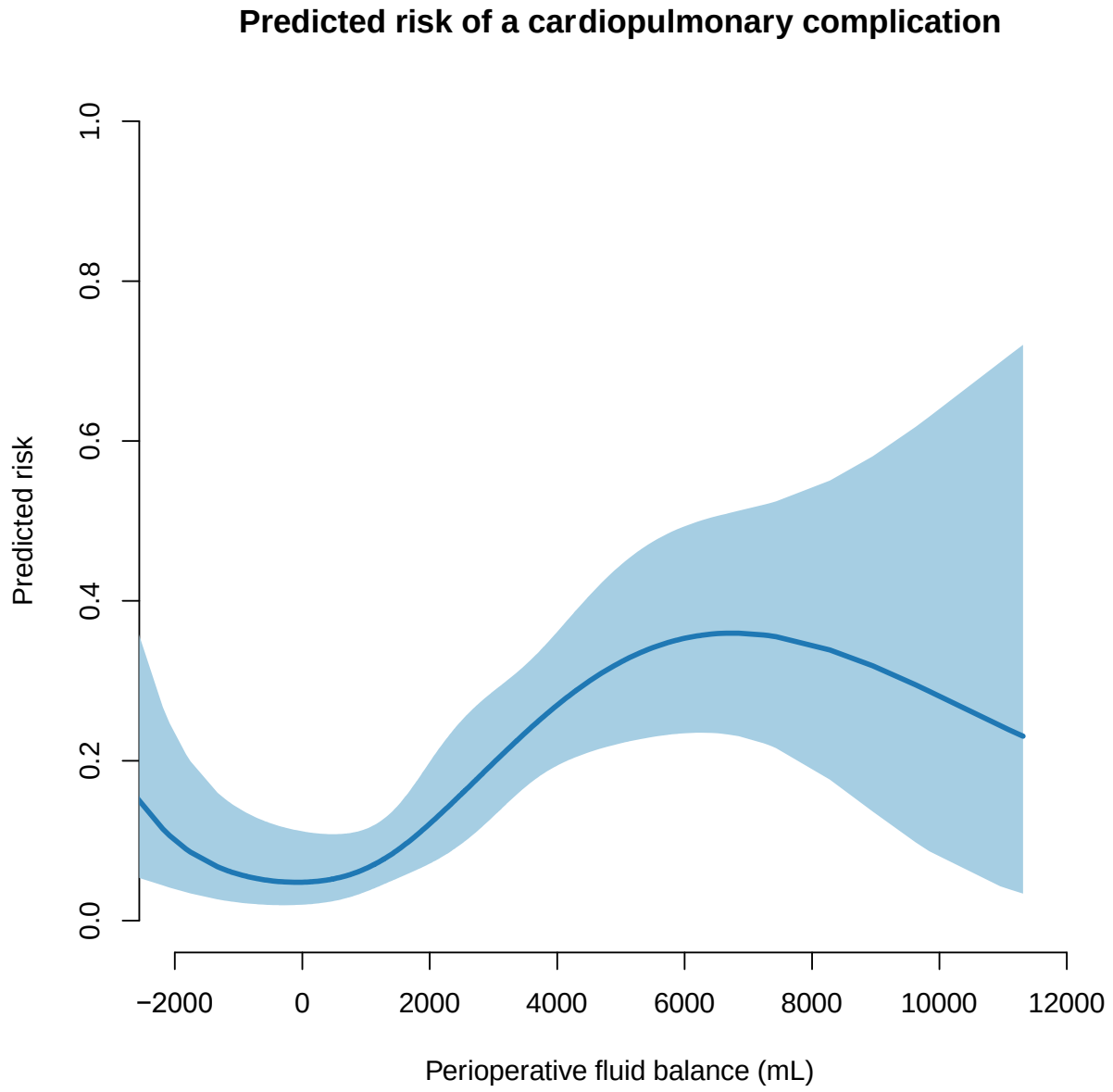
§ Fluid balance. * According to the 'Kidney Disease: Improving Global Outcome' (KDIGO) criteria deeming an increase of S-Creatinine by >26.5 mmol/L within 48 hours post-surgical.

Table 4. Logistic regression analysis on the association between the peri-operative fluid group and post-operative complications following emergency gastrointestinal surgery

	Low-FB§ group (fluid balance <0.0L)		Moderate-FB group (fluid balance 0.0-2.0L)	High-FB group (fluid balance >2.0L)	
	OR* (95% CI)	p value		OR (95% CI)	p value
			Crude analysis		
Primary outcome					
Cardiopulmonary complications	1.1 (0.3-3.6)	0.880	Ref#	3.4 (1.6-7.9)	0.002
Secondary outcome					
Renal complications	1.1 (0.3-3.3)	0.830	Ref	1.7 (0.8-3.9)	0.147
Infectious complications	0.8 (0.3-1.8)	0.598	Ref	1.2 (0.7-2.0)	0.605
Wound related complications	0.7 (0.3-1.9)	0.552	Ref	0.6 (0.3-1.2)	0.149
			Adjustedθ analysis		
Primary outcome					
Cardiopulmonary complications	1.7 (0.5-6.1)	0.436	Ref	3.4 (1.5-7.6)	0.002
Secondary outcome					
Renal complications	1.0 (0.5-1.7)	0.855	Ref	1.7 (0.8-3.6)	0.202
Infectious complications	0.8 (0.3-1.9)	0.571	Ref	1.0 (0.6-1.9)	0.852
Wound related complications	0.7 (0.3-2.2)	0.577	Ref	0.5 (0.3-1.2)	0.109

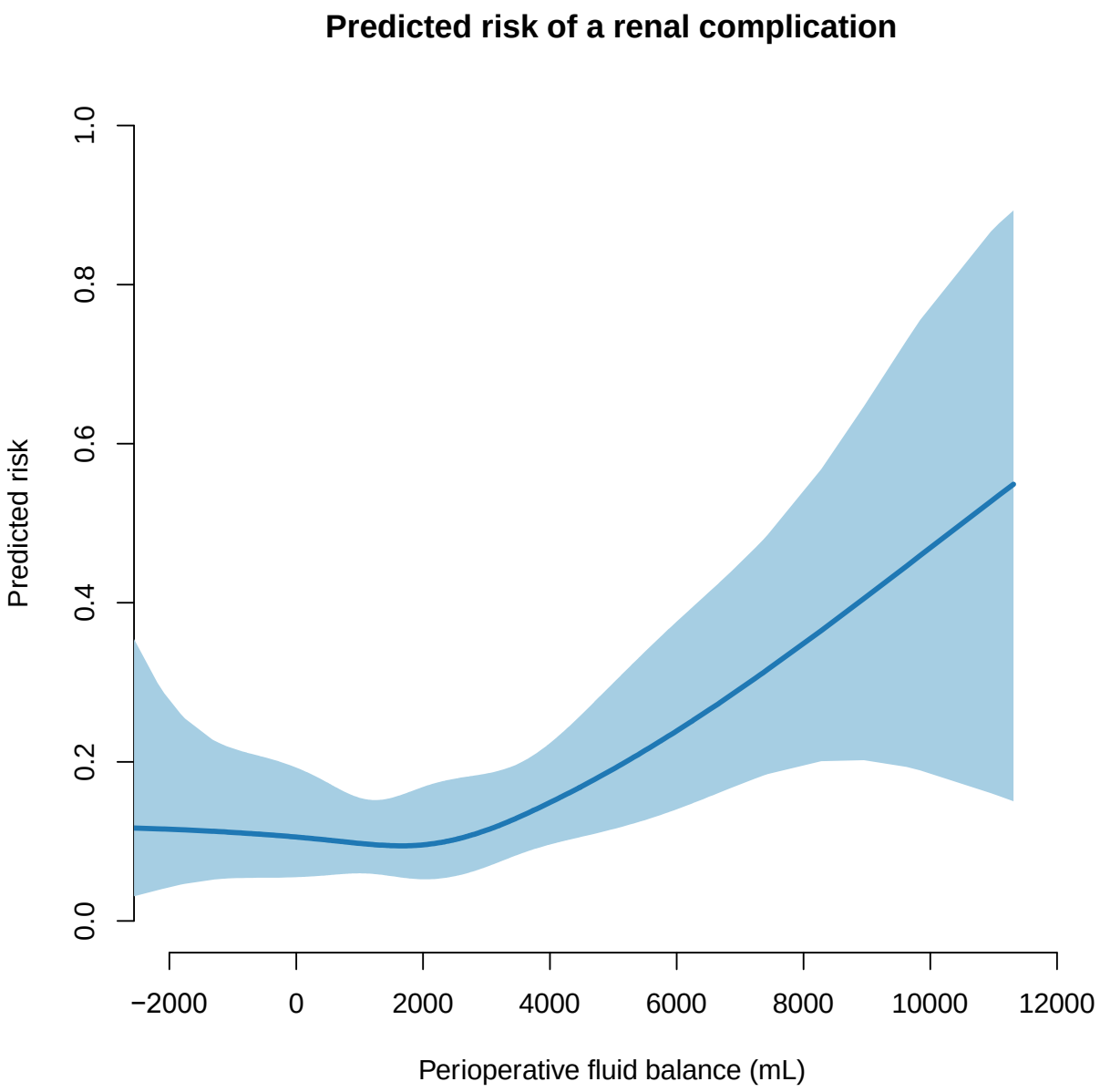
§ Fluid balance. * Odds ratio (95% confidence interval). # The Moderate-FB group serves as reference in bi-variate analysis. θ Adjusted by a weighted propensity score. A p-value <0.05 is considered significant.

Figure 1. The predicted risk of a cardiopulmonary complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect is p<0.001 and the non-parametric effect is p=0.008. The parametric calculation tests whether the fluid balance is linear associated with complications. The non-parametric analysis tests whether smoothing splines adds further precision to a linear relation of the model. A p-value <0.05 is considered significant.

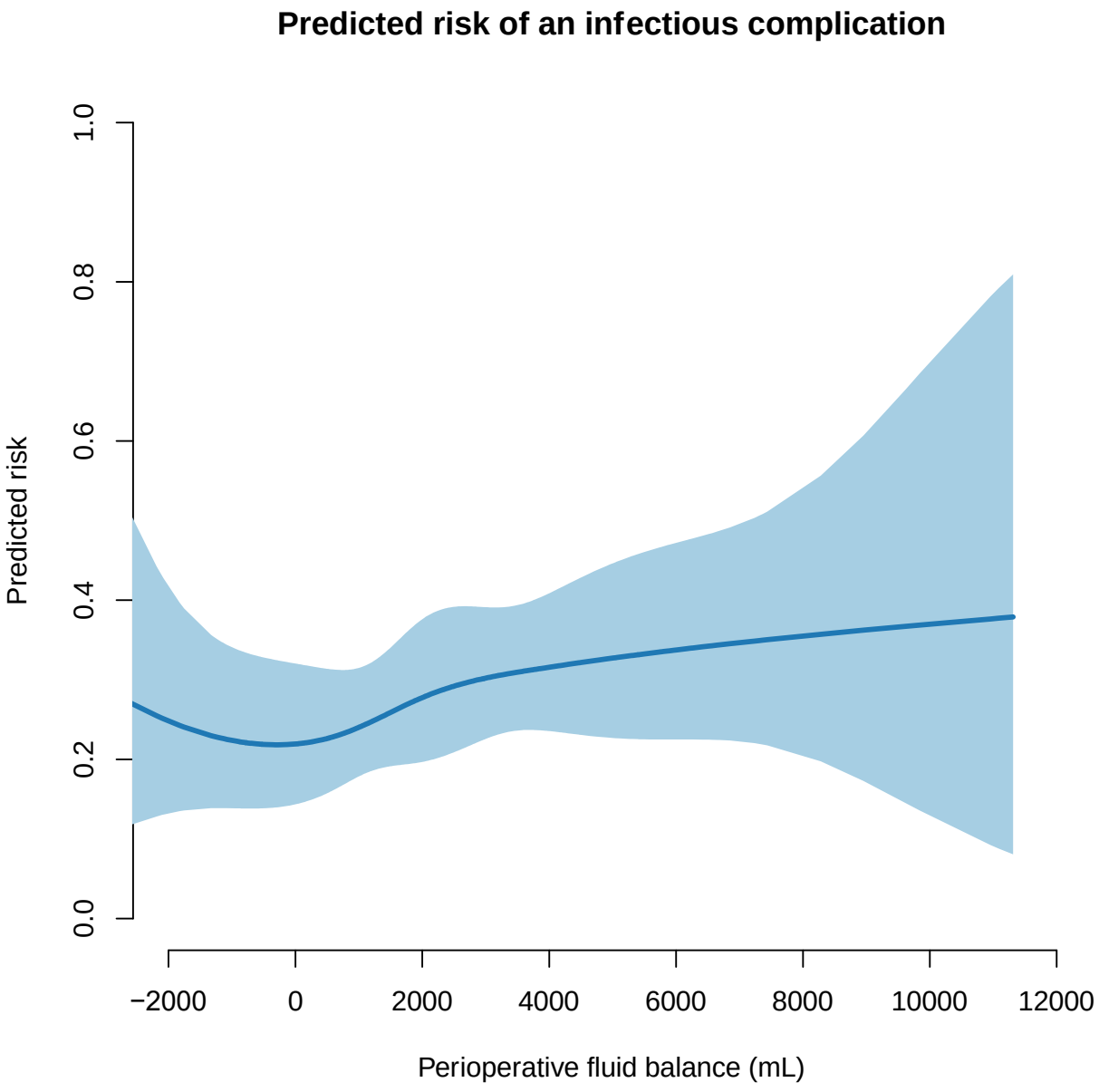
Figure 2. The predicted risk of a renal complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect is p=0.004 and the non-parametric effect is p=0.334. The parametric calculation tests whether the fluid balance is linear associated with complications. The non-parametric analysis tests whether smoothing splines adds further precision to a linear relation of the model. A p-value <0.05 is considered significant.

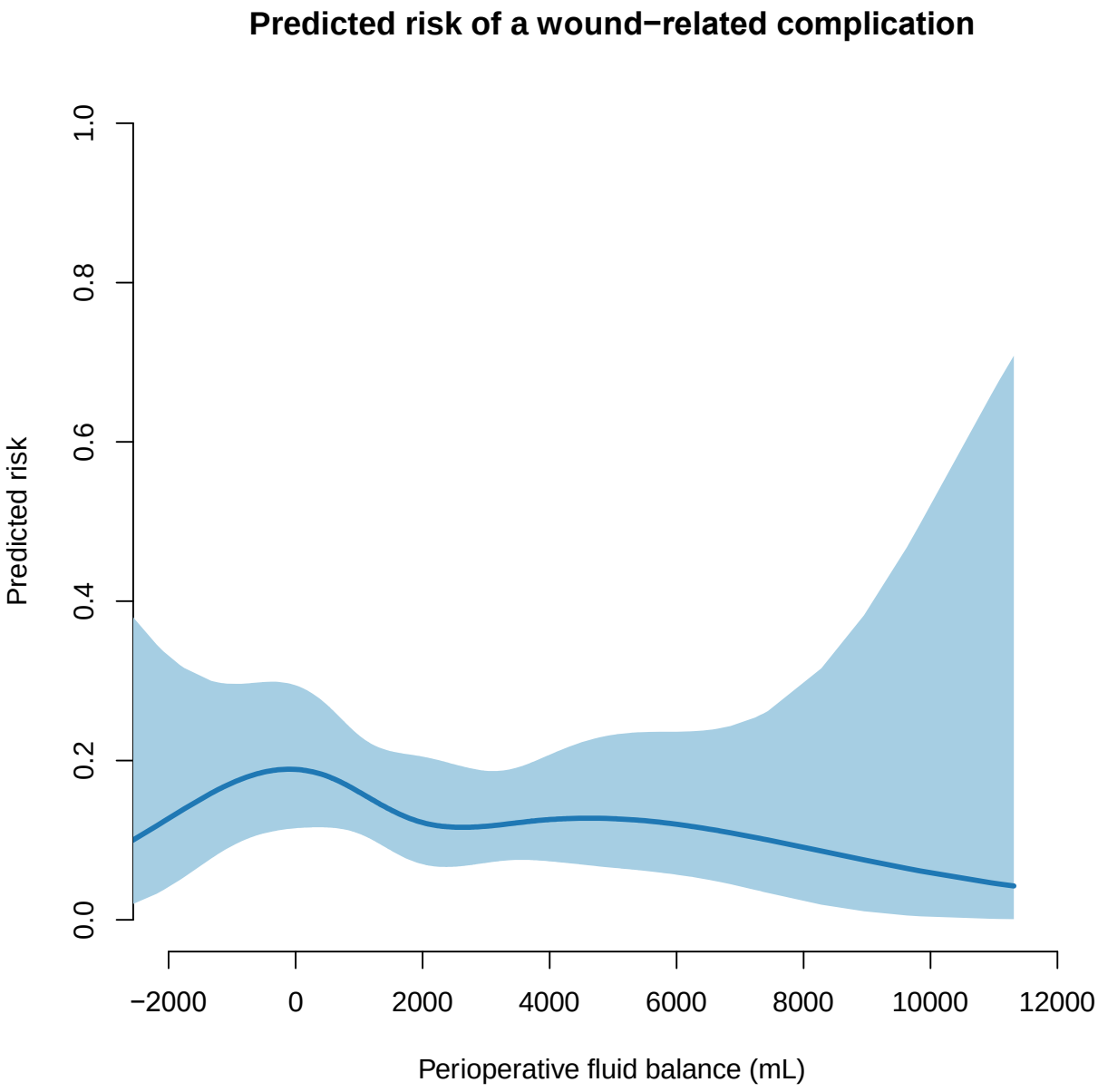
SUPPLEMENTARY MATERIAL

Supplementary Figure 1. The predicted risk of an infectious complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect is p=0.162 and the non-parametric effect is p=0.680. The parametric calculation tests whether the fluid balance is linear associated with complications. The non-parametric analysis tests whether smoothing splines adds further precision to a linear relation of the model. A p-value <0.05 is considered significant.

Supplementary Figure 2. The predicted risk of a wound complication associated with the peri-operative fluid balance following emergency gastrointestinal surgery



The blue line shows the predicted risk of a complication. The shaded area is the 95% confidence interval. We used a generalised additive model with smoothing splines and four degrees of freedom. The parametric effect is p=0.386 and the non-parametric effect is p=0.412. The parametric calculation tests whether the fluid balance is linear associated with complications. The non-parametric analysis tests whether smoothing splines adds further precision to a linear relation of the model. A p-value <0.05 is considered significant.

8.3 Paper III

Complications and Their Association with Mortality Following Emergency Gastrointestinal Surgery - an Observational Study

Title: Complications and Their Association with Mortality Following Emergency Gastrointestinal Surgery - an Observational Study

Short running title: Complications and Mortality in Emergency Gastrointestinal Surgery

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Category

Original article, retrospective cohort study.

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Conflicts of interest: The authors declare that they have no competing interests.

Keywords: Colorectal surgery, emergency, perioperative care, complications, outcomes.

ABSTRACT

Background

Emergency gastrointestinal surgery is followed by a high risk of major complications and death. The study's aim was to identify which complications that were strongest associated with death following emergency surgery for gastrointestinal obstruction or perforation.

Methods

We retrospectively included adult patients undergoing emergency gastrointestinal surgery with radiologically verified obstruction or perforation from three hospitals in Denmark. The exposure variables were 16 predefined Clavien-Dindo graded complications. Cox regression with delayed entry analysed the association with 90-day mortality. Adjustment was made for hospital, age, American Society of Anesthesiologists classification, pre-operative sepsis-2 score, cardiac comorbidity, renal comorbidity, hypertension, active cancer, bowel obstruction or perforation, and the surgical procedure. Subgroup analysis was made for patients with gastrointestinal obstruction or perforation.

Results

We included 349 patients operated between 2014 and 2015. In all, 281 (80.5%) patients had a complication. The risk of death was 20.6% (14) for patients with no complications and varied between 21-57% for patients with complications. Renal impairment (hazard ratio (HR): 6.8 (95%CI: 3.7-12.4)), arterial thromboembolic events (HR 4.8 (2.3-9.9)), and atrial fibrillation (HR 4.4 (2.8-6.8)) showed the strongest association with 90-day mortality. Atrial fibrillation was the only complication significantly associated with death in patients with gastrointestinal obstruction as well as perforation.

Conclusion

In this study of patients undergoing emergency gastrointestinal surgery, we found that renal impairment, arterial thromboembolic events, and atrial fibrillation were strongest associated with death. Atrial fibrillation might serve as an in-situ marker of patients needing escalation of care.

Introduction

Emergency abdominal surgery is followed by a substantial risk of postoperative complications which influence on the risk of death approximating 15-25%. [1–3] Complications develop in more than 30% of the patients and vary according to patient characteristics, the underlying pathology, and hospital characteristics. [4–6] Adverse events often prolong the hospital stay and postoperative complications are stronger associated with mortality than pre- and intra-operative variables. [7,8] A recent study found major complications in 47% of patients following emergency laparotomy for gastrointestinal obstruction, perforation, or bleeding and a mortality risk of 26%. [9] The risk of major cardiac and pulmonary complications was high the first days after surgery as was the risk of death. However, little is known about which postoperative complications that most strongly associate with death following emergency gastrointestinal (GI) surgery.

The association between postoperative complications and death has been addressed in several cohorts within elective surgery. The risk of death in patients with major postoperative complications is referred to as failure-to-rescue (FTR). FTR has been proven to efficiently evaluate the postoperative course on an institutional level allowing for the development of post hoc protocols to optimise care. FTR-metrics was originally developed for planned surgical procedures with a low risk of complications or death. [10] The complications included in the FTR-metric vary between studies and surgical areas. FTR is only gradually implemented in the area of emergency surgery, [11–14] thus expanding to patients with different diagnoses. Moreover, the incidence, the type, and the severity of complications following emergency surgery may differ considerably from elective cohorts and is likely to affect the association of specific postoperative complications and death. Importantly, specific post-operative complications might serve as valuable in situ markers of when to escalate care to prevent a fatal outcome.

Different complications appear at different times in the postoperative course as does death. As such, the association of a complication and death need to consider the time without a complication (un-exposed) and the time from a debuting complication to death (exposed). Not taking this into account may lead to the bias known as ‘immortal time bias’. Considering the ‘un-exposed’ time and the ‘exposed’ time may add important understanding of the association between individual complications with death following the event full course of emergency gastrointestinal surgery.

We hypothesised that complications evolve in continuums and that certain complications are stronger associated with 90-days mortality than others following emergency gastrointestinal surgery. Further, some

complications may serve as markers of an evolving adverse course independently of the underlying pathology. Identifying these index complications may offer as an in-situ marker of patients needing escalation of care. The aim of this study was to identify which postoperative complications that are strongest associated with death following emergency surgery for gastrointestinal obstruction or perforation.

Methods

This study was approved by the Ethical Committee (J.nr. 16-000014), Region Zealand, Denmark. The requirement for written informed consent was waived by the committee. Approval by the Danish Data Protection Agency (REG-149-2016) and the Danish Patient Safety Authority (3-3013-1999/1) was granted. We retrospectively included all patients scheduled for emergency gastrointestinal surgery, between 1 July 2014 and 31 July 2015 at three Hospitals in Region Zealand, Denmark. The hospitals treat all emergency cases among 800,000 citizens. In Denmark, emergency treatment is offered free of charge at public hospitals with no private alternative. The manuscript adheres to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement. [15]

We included patients aged 18 years or older who underwent emergency surgery for gastrointestinal obstruction or perforation, diagnosed by radiological examination. Thus, appendectomies, cholecystectomies, and surgery on the spleen or liver were not included. Emergency surgery was defined as the need for laparoscopy or laparotomy without planned delay. We excluded patients who had had intraabdominal surgery up to 30 days prior to the index procedure, patients with an iatrogenic or traumatic perforation, patients pregnant at the time of surgery, or patients in chronic dialysis. Patients eligible for inclusion more than once were only included at the first procedure. Only Danish residents were included.

We manually screened all patients planned for gastrointestinal surgery in the electronic booking system used at the participating hospitals. All emergent procedures due to obstruction, perforation, or undescribed cases were identified with the patients' personal identification number, allowing for data collection from the electronic patient files. Data from the pre-, intra-, and postoperative course were collected. The postoperative follow-up was 90 days on complications and mortality. Mortality data completeness was achieved through the Danish Civil Registration System. Data were collected between June 15, 2017 and March 31, 2018.

Data extraction was performed by clinically experienced medical staff trained in the use of the case report form and the Clavien-Dindo classification (CDC). [16] All patient files were accessed by two independent researchers and data collected in two separate case report forms. Case report forms were regularly assessed by the project leader (AWV) to settle disagreements. Minor variations were solved by the project leader, major inconsistencies were settled in dialogue between the project leader and the senior consultant responsible for the study (BB). Double data entry was performed, and irregularities corrected according to the case report form. Finally, range check was performed for all data.

The preoperative data collected were age, sex, smoking and alcohol habits, height, weight, co-morbidity (hypertension, cardiac, pulmonary, renal, diabetes, or presence of active cancer), American Society of Anaesthesiologists physical status classification (ASA class), sepsis-2 score, description of the radiological examinations, and time-to-surgery defined as time from decision of surgery to surgery. The intraoperative variables collected were time of surgery, the procedure performed, the intraabdominal pathology, intravenous fluid administration, and blood loss. The postoperative variables collected were sepsis-2 score, length of hospital stay, re-admissions, and in-hospital complications defined according to Table 1. The severity of complications was graded according to the CDC and only complications occurring postoperatively were registered. Death or cardiac arrest was not registered as a complication due to the study aim. Preoperative conditions were evaluated and only in case of substantial postoperative worsening, the condition was registered as a complication (increase in CDC class): [17] e.g. medically treated pneumonia preoperatively was only registered as a complication if it deemed mechanically respiratory support postoperatively. The date of appearance was used for complications but the most severe CDC graded the complication.

The primary exposure variable was 16 predefined complications (Table 1). We combined some individual complications considered to evolve in continuum or with similar treatment profiles. The follow-up on complications was contemplated as 90 days for all complications as the majority of complications demanded hospital admission. Planned operations were not regarded a complication, for example “second-look” or change of vacuum-assisted coverings. The primary outcome was 90-day all-cause mortality.

Statistics

Parametric and non-parametric statistics were used as appropriate. We presented events of complications as numbers and absolute risks. All-cause mortality was presented as relative risk for individual groups of complications (modified FTR). The primary outcome was analysed using a multivariable Cox proportional hazards model. To evaluate the influence of the first complication on mortality, we delayed the entry time to the date of the complication, i.e. the patient was included as non-exposed (no complication) before that date thereby avoiding immortal time bias. [18] A patient that did not die within the predefined 90 days was censored. The model presumes a progressive time span between a complication and death. Some complications appeared on the same day as death. Thus, half a day was added to the day of death or censoring. In case of a missing date on a complication the median time from surgery to the same complication in the cohort was used or the time to death in case it appeared first.

We created a multivariable model adjusting for variables significantly ($p<0.05$) associated with death in a univariable cox regression model with delayed entry. All variables demonstrating a significant association were included in the model. Several significant variables were found (Supplementary Table 1-11) and post hoc we decided to restrain the adjusted analysis to complications evolving in more than 40 patients to avoid overparameterization. Independent variables in the model were: hospital, age, ASA class (categorised in class 1-2 or 3-5), pre-operative sepsis-2 score (categorised as group 0-2 or 3-4), cardiac co-morbidity (yes or no), hypertension (yes or no), renal co-morbidity (yes or no), active cancer (yes or no), the diagnosis (bowel obstruction or perforation), and the type of surgery (bowel resection and stoma formation or other procedures). Three preoperative sepsis-2 scores were missing. Data on all other independent variables were complete. Post hoc, we decided to replace the missing preoperative sepsis-2 scores by the postoperative sepsis-2 score subtracted the median increase in sepsis-2 score (1.0 (IQR 1.0-2.0)) between the pre- and postoperative course. Test for linearity demonstrated a better fit for age in the potency. Proportionality was tested using Schoenfeldt residuals. The proportionality assumption was violated by the variable ´active cancer'; hence, the baseline hazard was stratified by the 'active cancer'-group. We performed subgroup analyses for patients with gastrointestinal obstruction or perforation. Bonferroni correction was used based on 16 outcomes and a two-sided p-value of < 0.003 was considered significant. We used R version 3.5.0 GUI 1.70 El Capitan ©R Foundation for Statistical Computing, 2016 and RStudio version 1.1.453 for the statistical analysis.

Results

A total of 349 patients were included in the analysis (Figure 1). The follow up on complications and death was complete (31,410 patient days) due to the patient files system linked to the Danish Civil Registration System. [19]

We registered 832 complications during the 90-day follow-up. Of the 349 patients analysed, 281 (80.5%) had a complication. Patients with a complication were more likely to have a higher ASA class, a diagnosis of gastrointestinal perforation, and a longer stay at the postoperative ward (Table 2). Dates were missing for 35 (4.2%) complications (Table 3). The median time to the first appearing complication was 3.0 days (IQR 1-4).

On the day of surgery and the first postoperative day (POD) 105 (12.6%) complications were registered and 19 (20.9%) deaths (Table 3). A total of 420 (50.5%) complications appeared between POD 2 to 7; 211 (25.4%) complications between POD 8 to 30; and 61 (7.3%) complications between POD 31 to 90. The incidence of complications was evenly distributed between POD 0-7 and POD 8-90 for deep wound complications (24 vs. 21), renal impairment (12 vs. 11), and re-operations (41 vs. 38). The majority of the following complications appeared late in the postoperative course (POD 0-7 vs. POD 8-90): superficial wound complications (25 vs. 51), peritonitis (8 vs. 16), urinary tract infection (10 vs. 30), pleural exudation (22 vs. 34), and venous thrombo-embolic events (1 vs. 5).

The overall risk of death was 26.1% (91) at 90-day follow-up. The patients who died tended to be older, have a higher ASA class or Sepsis-2 score preoperatively, presented with more cardiac or renal co-morbidity, and were more often known with active cancer than patients surviving (Table 2). Further, the patients had more often gastrointestinal perforation and anastomosis or stoma formation.

Complications and death

The risk of death was 20.6% (14) for patients with none of the registered complications and 27.4% (77) for patients with complications. In the group with no registered complications thirteen of the fourteen dead patients increased in sepsis-2 score after surgery and ten had septic shock and were dead within postoperative day one. The risk of death, according to the 16 individual complications (modified FTR), ranged from 21% in patients with prolonged paralysis and up to more than 50% for patients with renal impairment or atrial fibrillation (Table 4).

The crude Cox-regression analysis with delayed entry showed that out of ten significant associations renal impairment, arterial thromboembolic events, and atrial fibrillation where the complications most strongly associated with death (Table 4). The adjusted multivariable model showed seven significant associations out of eleven analysed complications. Atrial fibrillation (HR 3.3 (95%CI 2.1-5.2), p<0.001), deep wound complication (HR 3.2 (1.7-5.8), p<0.001), and respiratory failure (HR 2.9 (1.6-5.1), p<0.001) were most strongly associated with 90-day mortality (Table 4).

Of all patients, 87 (24.9%) had only one complication with a mortality risk of 14.9%, two complications appeared in 57 (16.3%) patients and the mortality risk was 17.5%, and three or more complications appeared in 137 (39.3%) patients with a mortality risk of 39.4%.

Gastrointestinal obstruction or perforation

In total, 261 patients had GI obstruction of whom 204 (78.2%) had one or more of 547 registered complications. The overall 90-day mortality risk was 21.8% (57). The risk of death was 15.8% (9) for patients with no complications and 23.5% (48) for patients with complications. Of the nine dead patients with no registered complications five had septic shock and were dead within postoperative day one. The crude Cox-regression model demonstrated ten complications significantly associated with 90-day mortality of which renal impairment, pulmonary oedema, and respiratory failure dominated (Table 5).

Eighty-eight patients had a gastrointestinal perforation of which 77 (87.5%) had one or more of 285 registered complications. The overall 90-day mortality risk was 38.6% (34). The risk of death was 45% (5) for patients with none of the registered complications and 37.7% (29) for patients with complications. Of the five dead patients with no registered complications, all had septic shock and were dead within postoperative day one. Atrial fibrillation was the only complication that was significantly associated with death in this sub-group of patients. In both subgroups the number of patients with the complications were small, and adjusted analysis were not performed.

Discussion

In this observational retrospective study of patients having emergency surgery for gastrointestinal obstruction or perforation, we found that 81% of the patients had complications of which 27% were dead at 90-day follow up. One-third of the complications debuted after the first week from surgery and the majority of patients had two or more complications. Renal impairment and arterial thromboembolic events were strongest associated with death, yet rare. In the adjusted analysis, the complications with the strongest association with death at 90-day follow up were atrial fibrillation, deep wound complications, and respiratory failure.

We found a significant association in 10 of 16 complications with death with varying hazard rates from 2.4 to 6.8 and a risk of death ranging from 32% to 57%. The variability supports our hypothesis that different complications correlate unevenly with death and emphasises that minor (e.g. atrial fibrillation) as well as major (e.g. renal impairment) complications are important in the postoperative course in the urgent setting.

The risk of death in patients with complications is known as failure-to-rescue (FTR). Initially introduced by Silber in 1992, arrhythmia was included in the FTR-metric. [10] Alternative definitions followed of which some focused on surgical complications (e.g. wound infection or re-operations) while others primarily include medical complications (pulmonary, cardiac, renal, infectious, or thromboembolic). [11,20] Interestingly, we found that atrial fibrillation and deep wound complication (fascia dehiscence and deep wound infection) demonstrated the highest and a similar hazard ratio to death. Fascia dehiscence was the primary reason for a re-operation in our cohort.

Re-operation was performed in 23% of the patients in our cohort with a mortality risk of 32% and showed to be strongly associated with death. The association has previously been documented following emergency laparotomy with incidence rates ranging from 20% to 36%. [4,21,22] However, the mortality risk varies vividly between 20% and 72%. It has been shown that re-operations are associated with an increased risk of medical complications, additional re-operations, and transfer to the intensive care unit and that each additional re-operation increases the risk of death. [23] These findings have several possible explanations: the surgical stress response is repeated, an inflammatory response amplified, and the side effects of intravenous fluid therapy, the anaesthesia and other drugs accumulate, and might accelerate an adverse outcome.

Re-operations are generally not optional. Not operating might have vital consequences and re-operations may be the only chance to rescue the patient. In our study, unplanned re-operations were dominated by fascia dehiscence. We found 11% with fascia dehiscence. The risk of fascia dehiscence varies between 3.8% and 28% following emergency laparotomy [21,24] and is associated with morbidity and death. [25,26] The risk of fascia dehiscence is associated with patient- and doctor-related factors. Dominating patient related factors are obesity, smoking habits, alcohol habits, the degree of contamination of the wound, the presence of peritonitis, or the presence of high postoperative intraabdominal pressure. The iatrogenic factors are choice of suture and sewing technique. One study found the risk of fascia dehiscence and subsequently death significantly decreased compared to a historical cohort, following implementation of a new suture and sewing technique in patients undergoing emergency laparotomy. [25] Moreover, the increasing share of laparoscopic surgical approach in emergency gastrointestinal surgery hold a potential to further reduce the risk of fascia dehiscence. [27]

A striking finding in our study was the marked association between atrial fibrillation and death. Even though we found that different complications dominate in patients with GI obstruction or GI perforation, atrial fibrillation uniformly demonstrated one of the strongest associations with death in both sub-groups of patients. Atrial fibrillation is the most common postoperative arrhythmia. The incidence varies according to the type of surgery ranging from 1.4% in non-cardiac surgery an up to more than 30% following cardiac surgery. [28,29] We found a risk of atrial fibrillation of 19% in our cohort. Post-operative atrial fibrillation has been associated with pre-operative patient characteristics as age, male sex, cardiopulmonary disease, hypertension, and pre-existing atrial fibrillation. [30]

The association between atrial fibrillation and a postoperative adverse course has been documented following oesophagostomies and cardiac surgery, while studies within gastrointestinal surgery are few. [31–33] Postoperative atrial fibrillation has previously been associated with sepsis, a leaking bowel anastomosis, a prolonged hospital stay, or death, [30,33–35] which support our finding. The pathophysiological relation is, however, not well understood, since it is unlikely that atrial fibrillation in itself is the mediator of various complications or death. The inflammatory response and the release of catecholamines following surgery has been argued to prompt postoperative atrial fibrillation. The association between atrial fibrillation and stroke or myocardial infarction has been documented and is a rational relation. [36] However, the association between atrial fibrillation and subsequent surgical complications is more difficult to explain. It has been argued that atrial fibrillation altars the circulation and may compromise blood flow at the surgical site. Another possible explanation is that perioperative intravenous fluid administration combined with a

hormonal stress response that retains fluid, causes oedema of the tissue and induces atrial fibrillation as well, which further accelerate the risk of pulmonary congestion and oedema of the surgical site with poor wound- and anastomosis healing. [37] Both mechanisms might explain why atrial fibrillation, appears in the early postoperative course while surgical complications evolve days to weeks later. Our results suggest that post-operative onset of atrial fibrillation should mediate a thorough assessment of the patient in search for an underlying pathology and may serve as an early marker of patients needing escalation of care.

The strengths of our study are the double data extraction and registration, clear definitions of study variables, and the analytical adjustment for delayed entry, which eludes immortal time bias. [18] The contribution from multiple sites increases the external validity and generalisability of the study results. The limitations of our study are inherent in the retrospective design, relying on patient files. We accommodated this by using clear definitions of complications and double registration of the prospectively collected data in a public health system ensuring 100% follow-up on mortality of all Danish residents. [19] Despite a clear definition of the cohort, different intraabdominal pathologies were disclosed and might influence differently on the risk of complications and death. However, we corrected for important confounders in the adjusted analysis; yet, some complications were rare, and the low numbers prevented an adjusted analysis. No matter the adjustment the result of this study is merely hypothesis generating leaving future randomised trial to investigate.

Conclusion

In this observational study of patients undergoing emergency surgery for gastrointestinal obstruction or perforation, we found that 80% of the patients had a complication and two-third of the complications appear within the first postoperative week. Renal impairment and arterial thromboembolic events were most strongly associated with death, however rare. Of the more frequent complications atrial fibrillation, deep wound complications, and respiratory failure were most strongly associated with death. Atrial fibrillation, was uniformly associated with death in both sub-groups of patients with gastrointestinal obstruction or perforation and may serve as an important early marker of patients needing escalation of care.

Authors' contributions

AWV: Developed the idea, obtaining legislative and ethical approvals, planned the study, searched the literature, drafted the protocol, collected the data, planned the analysis and interpretation, conducted the analysis, drafted the present manuscript, revised and approved the final manuscript. Raised the funds.
AAA, JB, and SE: Collected the data, revised the analysis and interpretation, revised and approved the final manuscript.
AWB, RL, SJ, and HE: Collected the data, interpreted the data, revised and approved the final manuscript.
LCT and AMM: Planned the study, refined the drafted protocol, planned the analysis, revised the analysis and interpretation, revised and approved the final manuscript.
BB: Planned the study, refined the drafted protocol, planned the analysis, revised the analysis and interpretation, revised and approved the final manuscript. Responsible for initiating and conducting the trial. Raised the funds.

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References

1. Saunders DI, Murray D, Pichel AC, Varley S, Peden CJ, UK Emergency Laparotomy Network. Variations in mortality after emergency laparotomy: the first report of the UK Emergency Laparotomy Network. *Br J Anaesth*. 2012;109(3):368-375. doi:10.1093/bja/aes165
2. Barrow E, Anderson ID, Varley S, et al. Current UK practice in emergency laparotomy. *Ann R Coll Surg Engl*. 2013;95(8):599-603. doi:10.1308/rcsann.2013.95.8.599
3. Symons NRA, Moorthy K, Almoudaris AM, et al. Mortality in high-risk emergency general surgical admissions. *Br J Surg*. 2013;100(10):1318-1325. doi:10.1002/bjs.9208
4. Iversen LH, Bülow S, Christensen IJ, Laurberg S, Harling H. Postoperative medical complications are the main cause of early death after emergency surgery for colonic cancer. *Br J Surg*. 2008;95:1012-1019. doi:10.1002/bjs.6114
5. Simões CM, Carmona MJC, Hajjar LA, et al. Predictors of major complications after elective abdominal surgery in cancer patients. *BMC Anesthesiol*. 2018;18(1):49. doi:10.1186/s12871-018-0516-6
6. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: A 7 day cohort study. *Lancet*. 2012;380(9847):1059-1065. doi:10.1016/S0140-6736(12)61148-9
7. McCoy CC, Englum BR, Keenan JE, Vaslef SN, Shapiro ML, Scarborough JE. Impact of specific postoperative complications on the outcomes of emergency general surgery patients. *J Trauma Acute Care Surg*. 2015;78(5):912-919. doi:10.1097/TA.0000000000000611
8. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005;242(3):326-341; discussion 341-3. doi:10.1097/01.sla.0000179621.33268.83
9. Tengberg LT, Cihoric M, Foss NB, et al. Complications after emergency laparotomy beyond the immediate postoperative period - a retrospective, observational cohort study of 1139 patients. *Anaesthesia*. 2017;72(3):309-316. doi:10.1111/anae.13721
10. Silber JH, Williams S V., Krakauer H, Schwartz JS. Hospital and patient characteristics associatedwith death after surgery: A study of adverse occurrence and failure to rescue. *Med Care*. 1992;30(7):615-627. doi:10.1097/00005650-199207000-00004
11. Holena DN, Kaufman EJ, Delgado MK, et al. A metric of our own: Failure to rescue after trauma. *J Trauma Acute Care Surg*. 2017;83(4):698-704. doi:10.1097/TA.0000000000001591
12. Metcalfe D, Castillo-Angeles M, Olufajo OA, et al. Failure to rescue and disparities in emergency general surgery. *J Surg Res*. 2018;231:62-68. doi:10.1016/j.jss.2018.04.047
13. Mehta A, Efron DT, Canner JK, et al. Effect of Surgeon and Hospital Volume on Emergency General Surgery Outcomes. *J Am Coll Surg*. 2017;225(5):666-675.e2. doi:10.1016/j.jamcollsurg.2017.08.009
14. Ghaferi AA, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. *Ann Surg*. 2009;250(6):1029-1033. doi:10.1097/SLA.0b013e3181bef697
15. Elm E von, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-808. doi:10.1136/bmj.39335.541782.AD
16. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae
17. Mentula PJ, Leppäniemi AK. Applicability of the Clavien-Dindo classification to emergency surgical procedures: a retrospective cohort study on 444 consecutive patients. *Patient Saf Surg*. 2014;8(1):31. doi:10.1186/1754-9493-8-31
18. Hanley JA, Foster BJ. Avoiding blunders involving “immortal time.” *Int J Epidemiol*. 2014;43(3):949-961. doi:10.1093/ije/dyu105
19. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7_suppl):22-25. doi:10.1177/1403494810387965
20. Johnston MJ, Arora S, King D, et al. A systematic review to identify the factors that affect failure to rescue and escalation of care in surgery. *Surgery*. 2015;157(4):752-763. doi:10.1016/j.surg.2014.10.017
21. Kim JJ, Liang MK, Subramanian A, Balentine CJ, Sansgiry S, Awad SS. Predictors of relaparotomy after nontrauma emergency general surgery with initial fascial closure. *Am J Surg*. 2011;202(5):549-552. doi:10.1016/j.amjsurg.2011.06.023
22. Kassahun WT, Mehdorn M, Wagner TC. The effects of reoperation on surgical outcomes following surgery for

major abdominal emergencies. A retrospective cohort study. *Int J Surg*. 2019;72:235-240. doi:10.1016/j.ijsu.2019.11.024
23. Martínez-Casas I, Sancho JJ, Nve E, Pons MJ, Membrilla E, Grande L. Preoperative risk factors for mortality after relaparotomy: Analysis of 254 patients. *Langenbeck's Arch Surg*. 2010;395(5):527-534. doi:10.1007/s00423-009-0538-0
24. Marwah S, Marwah N, Singh M, Kapoor A, Karwasra RK. Addition of rectus sheath relaxation incisions to emergency midline laparotomy for peritonitis to prevent fascial dehiscence. *World J Surg*. 2005;29(2):235-239. doi:10.1007/s00268-004-7538-6
25. Tolstrup M-B, Watt SK, Gögenur I. Reduced Rate of Dehiscence After Implementation of a Standardized Fascial Closure Technique in Patients Undergoing Emergency Laparotomy. *Ann Surg*. 2017;265(4):821-826. doi:10.1097/SLA.0000000000001762
26. van Ramshorst GH, Eker HH, van der Voet JA, Jeekel J, Lange JF. Long-Term Outcome Study in Patients with Abdominal Wound Dehiscence: A Comparative Study on Quality of Life, Body Image, and Incisional Hernia. *J Gastrointest Surg*. 2013;17(8):1477-1484. doi:10.1007/s11605-013-2233-2
27. Agresta F, Campanile FC, Podda M, et al. Current status of laparoscopy for acute abdomen in Italy: a critical appraisal of 2012 clinical guidelines from two consecutive nationwide surveys with analysis of 271,323 cases over 5 years. *Surg Endosc*. 2017;31(4):1785-1795. doi:10.1007/s00464-016-5175-4
28. Gialdini G, Nearing K, Bhave PD, et al. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA - J Am Med Assoc*. 2014;312(6):616-622. doi:10.1001/jama.2014.9143
29. Maesen B, Nijs J, Maessen J, Allessie M, Schotten U. Post-operative atrial fibrillation: A maze of mechanisms. *Europace*. 2012;14(2):159-174. doi:10.1093/europace/eur208
30. Bhave PD, Goldman LE, Vittinghoff E, Maselli J, Auerbach A. Incidence, predictors, and outcomes associated with postoperative atrial fibrillation after major noncardiac surgery. *Am Heart J*. 2012;164(6):918-924. doi:10.1016/j.ahj.2012.09.004
31. Schizas D, Kosmopoulos M, Giannopoulos S, et al. Meta-analysis of risk factors and complications associated with atrial fibrillation after oesophagectomy. *Br J Surg*. 2019;106(5):534-547. doi:10.1002/bjs.11128
32. Lomivorotov V V., Efremov SM, Pokushalov EA, Karaskov AM. New-Onset Atrial Fibrillation after Cardiac Surgery: Pathophysiology, Prophylaxis, and Treatment. *J Cardiothorac Vasc Anesth*. 2016;30(1):200-216. doi:10.1053/j.jvca.2015.08.003
33. Walsh SR, Oates JE, Anderson JA, Blair SD, Makin CA, Walsh CJ. Postoperative arrhythmias in colorectal surgical patients: Incidence and clinical correlates. *Color Dis*. 2006;8(3):212-216. doi:10.1111/j.1463-1318.2005.00881.x
34. Wells CI, Robertson JP, Campbell S, Al-Herz F, Rhind B, Young M. Impact of atrial fibrillation on long-term survival following oesophagectomy: a 21-year observational study. *ANZ J Surg*. 2018;88(4):E268-E272. doi:10.1111/ans.14054
35. Siu CW, Tung HM, Chu KW, Jim MH, Lau CP, Tse HF. Prevalence and predictors of new-onset atrial fibrillation after elective surgery for colorectal cancer. *PACE - Pacing Clin Electrophysiol*. 2005;28(SUPPL. 1). doi:10.1111/j.1540-8159.2005.00024.x
36. AlTurki A, Marafi M, Proietti R, et al. Major adverse cardiovascular events associated with postoperative atrial fibrillation after noncardiac surgery a systematic review and meta-analysis. *Circ Arrhythmia Electrophysiol*. 2020;13(1):71-80. doi:10.1161/CIRCEP.119.007437
37. Marjanovic G, Villain C, Juettner E, et al. Impact of Different Crystalloid Volume Regimes on Intestinal Anastomotic Stability. *Ann Surg*. 2009;249(2):181-185. doi:10.1097/SLA.0b013e31818b73dc

Table 1 – Definition of postoperative complications

Complication	Variable	Definition
Superficial wound complication	Superficial wound rupture	Conservative or surgical treatment
	Superficial wound infection	Wound rupture, a need for removal of infected tissue, or medical treatment
Deep wound complication	Deep wound infection and fascial defect	A need for surgical cleavage or removal of infected tissue with fascial defect
	Fascia dehiscence	Spontaneous fascial rupture with a need for re-operation
Peritonitis	Peritonitis	Debut postoperatively
	Intraabdominal abscess	Suspected radiologically and with a need for surgical or medical treatment
Prolonged paralysis	Prolonged paralysis of intestine	≥4 days without defecation
GI bleeding	Gastrointestinal bleeding	A need for surgical or endoscopic treatment
Packed blood products		Transfusion with packed blood, thrombocytes, or plasma
Pneumonia		Diagnosed by the treating physician and medical treatment initiated
Urinary tract infection		Diagnosed by the treating physician and medical treatment initiated
Atrial fibrillation		Verified by electrocardiogram and a need for treatment
Pleural exudation	Exudation to the pleural cavity	Verified by radiology
Pulmonary oedema	Pulmonary congestion	With a need for medical treatment
	Pulmonary oedema	Radiographic suspicion and a need for intensive care
Respiratory failure	CPAP	A need for non-invasive ventilation or continuous positive airway pressure (CPAP) after the day of extubation
	Failure to wean	Intubation continued for more than 48 hours after surgery
	Re-intubation	Re-intubation of any cause
Venous thrombo-embolic event	Deep venous thrombosis	Verified by radiology
	Pulmonary embolism	Verified by scintigraphy or CT-scan
Arterial thrombo-embolic event	Acute myocardial infarction	ECG-pathology and treatment initiated
	Stroke	Relevant radiology or diagnosed by neurologist
	Disseminated intravascular coagulopathy	Diagnosed by the treating physician
Renal impairment	Renal failure	A need for dialysis with or without treatment
	Other renal	Hydronephrosis or nephritis
Re-operation	Superficial wound rupture or infection	With a need for surgical intervention
	Fascial rupture	Spontaneous fascial rupture with a need for intraabdominal surgery
	Separation of stoma	Requiring intraabdominal surgery
	Anastomosis leakage	Requiring intraabdominal surgery
	Re-perforation	Requiring intraabdominal surgery
	Peritonitis or abscess	Requiring intraabdominal surgery
	Postoperative obstruction of intestine	Requiring intraabdominal surgery
	Gastrointestinal bleeding	Intraabdominal surgery pro haemostasis

Figure 1. Trial profile

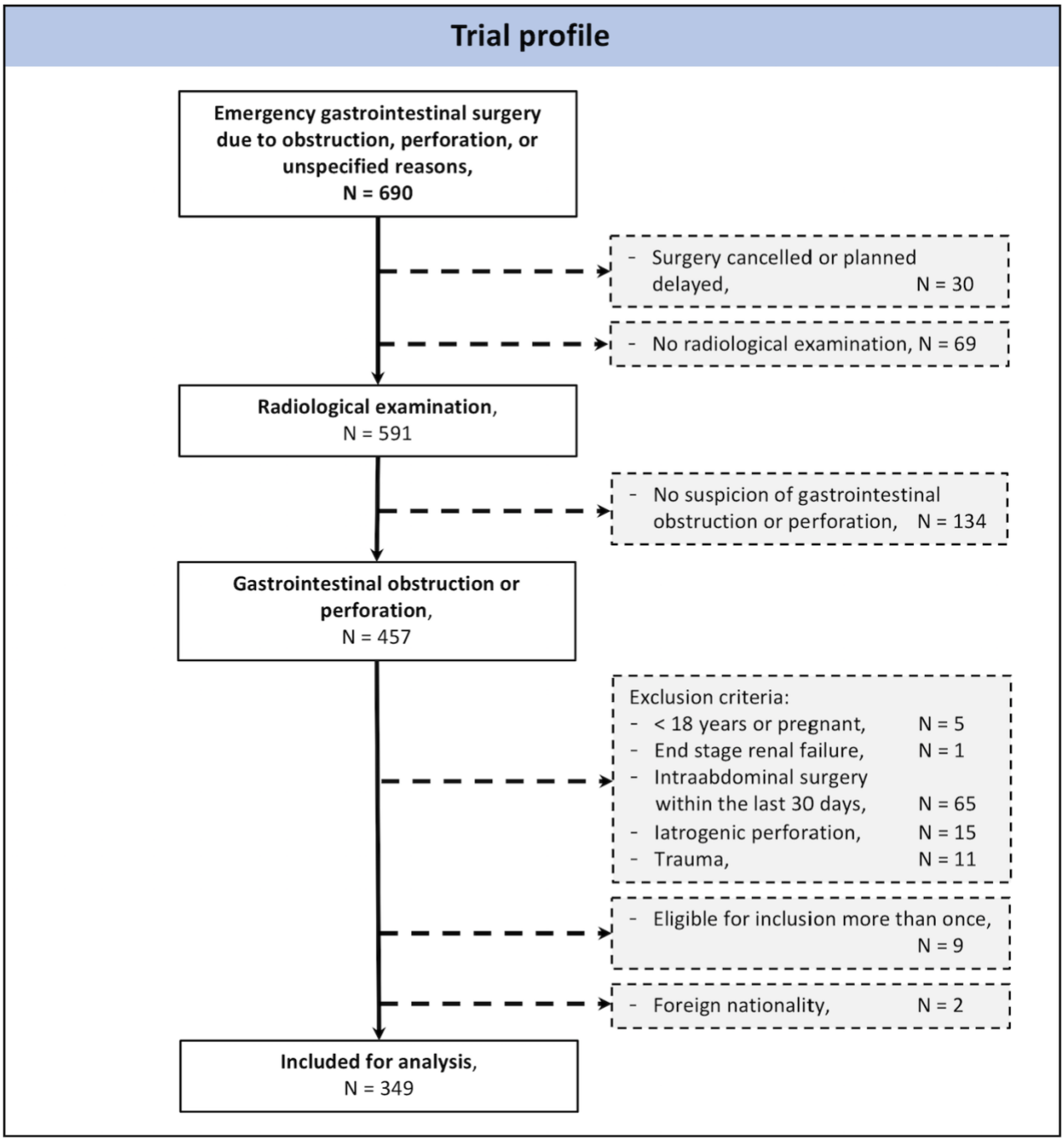

Table 2 – Background characteristics according the incidence of complications or death.

	Patients with no complication	Patients with a complication	Alive at follow up	Dead at follow up
Number of patients	68	281	258	91
Sex, female, No (%)	40 (58.8)	157 (55.9)	142 (55.0)	55 (60.4)
Age, years, median [IQR$_{\varphi}$]	71.5 [57.8, 79.8]	71.0 [63.0, 79.0]	69.0 [59.2, 77.0]	77.0 [71.5, 83.0]
BMI[§], median [IQR]	25.0 [20.7, 28.8]	23.9 [21.3, 27.1]	24.1 [21.3, 28.0]	23.6 [20.8, 26.6]
Missing, No	8	19	22	5
Actively smoking, No (%)	18 (28.6)	95 (34.5)	87 (35.1)	26 (28.9)
Missing, No	5	6	10	1
Excess alcohol intake[#], No (%)	4 (6.2)	36 (13.3)	32 (13.0)	8 (9.2)
Missing, No	4	11	11	4
ASA-class*, No (%)				
Class 0-2	43 (63.2)	146 (52.0)	168 (65.1)	21 (23.1)
Class 3-5	25 (36.8)	135 (48.0)	90 (34.9)	70 (76.9)
Sepsis-2 score, pre-operative, No (%)				
group 0-2	42 (61.8)	152 (54.1)	161 (62.9)	31 (34.4)
group 3-4	26 (38.2)	129 (45.9)	95 (37.1)	59 (65.6)
Co-existing diseases, No (%)				
Cardiac comorbidity	17 (25.0)	81 (28.8)	64 (24.8)	34 (37.4)
Hypertension	31 (45.6)	124 (44.1)	107 (41.5)	48 (52.7)
Pulmonary comorbidity	10 (14.7)	49 (17.4)	41 (15.9)	18 (19.8)
Renal comorbidity	2 (2.9)	26 (9.3)	13 (5.0)	15 (16.5)
Diabetes mellitus	7 (10.3)	42 (14.9)	36 (14.0)	13 (14.3)
Active cancer	11 (16.2)	43 (15.3)	29 (11.2)	25 (27.5)
Intraabdominal pathology, No (%)				
Adhesions	34 (50.0)	122 (43.4)	132 (51.2)	24 (26.4)
Ulcer disease	3 (4.4)	25 (8.9)	18 (7.0)	10 (11.0)
Diverticulitis	5 (7.4)	24 (8.5)	21 (8.1)	8 (8.8)
Intraabdominal cancer	9 (13.2)	46 (16.4)	29 (11.2)	26 (28.6)
Hernia	2 (2.9)	12 (4.3)	10 (3.9)	4 (4.4)
Crohn disease	3 (4.4)	2 (0.7)	4 (1.6)	1 (1.1)
Vascular ischemia	4 (5.9)	5 (1.8)	5 (1.9)	4 (4.4)
Volvulus	2 (2.9)	19 (6.8)	17 (6.6)	4 (4.4)
Other	6 (8.8)	26 (9.3)	22 (8.5)	10 (11.0)
Surgical indication, No (%)				
GI[¤] obstruction	57 (83.8)	204 (72.6)	204 (79.1)	57 (62.6)
GI perforation	11 (16.2)	77 (27.4)	54 (20.9)	34 (37.4)
Time to surgery, median [IQR]	4.0 [2.8, 6.0]	3.0 [2.0, 6.0]	3.0 [2.0, 6.0]	3.0 [2.0, 5.0]
Intra- and post-operative course				
Surgical access, No (%)				
Laparoscopy	6 (8.8)	16 (5.7)	18 (7.0)	4 (4.4)
Laparotomy	62 (91.2)	265 (94.3)	240 (93.0)	87 (95.6)
Surgical procedure, No (%)				
Other procedure	32 (47.1)	122 (43.4)	128 (49.6)	26 (28.6)
Bowel resection and stoma formation	36 (52.9)	159 (56.6)	130 (50.4)	65 (71.4)
Fluid administration, mL, median (IQR)	1800 [1080, 2240]	2140 [1470, 3140]	1940 [1280, 2720]	2330 [1560, 3210]
Missing, No	0	1	0	1
Blood-loss, mL, median [IQR]	0 [0, 100]	50 [0, 300]	0 [0, 250]	50 [0, 300]
Time of surgery, hour, median [IQR]	1.6 [1.0, 2.2]	1.9 [1.4, 2.8]	1.8 [1.3, 2.6]	2.0 [1.4, 2.9]
Missing, No	0	7	7	0
Time at recovery room, hour median [IQR]	3.0 [2.0, 6.0]	6.0 [3.0, 12.0]	5.0 [3.0, 11.0]	6.0 [3.0, 12.0]
Missing, No	2	3	1	4

φ Inter-quartile range. § Body mass index. # >7 drinks/week for women or >14 drinks/week for men. * American Society of Anesthesiologists Classification of physical status. ¤ Gastrointestinal.

Table 3. Number of patients with a complication according to the postoperative day (POD).

Complication	Events / missing dates	POD 0-1	POD 2-7	POD 8-14	POD 15-30	POD 31-90
		Patients with a complication, No (%)				
Superficial wound complication	81 / 5	5 (6.2)	20 (24.7)	22 (27.2)	22 (27.2)	7 (8.6)
Superficial wound rupture	43					
Superficial wound infection	38					
Deep wound complication	45 / 0	1 (2.2)	23 (51.1)	16 (35.6)	4 (8.9)	1 (2.2)
Deep wound infection	5					
Fascia dehiscence	40					
Peritonitis	24 / 0	0 (0.0)	8 (33.3)	8 (33.3)	7 (29.2)	1 (4.2)
Peritonitis	4					
Intraabdominal abscess	20					
Prolonged paralysis	145 / 0	-	145 (100.0)	-	-	-
Gastrointestinal bleeding	19 / 0	5 (26.3)	6 (31.6)	4 (21.1)	2 (10.5)	2 (10.5)
Packed blood-products	47 / 6	12 (25.5)	24 (51.1)	3 (6.4)	2 (4.3)	0 (0.0)
Pneumonia	110 / 6	21 (19.1)	48 (43.6)	21 (19.1)	8 (7.3)	6 (5.5)
Urinary tract infection	44 / 4	3 (6.8)	7 (15.9)	6 (13.6)	12 (27.3)	12 (27.3)
Atrial fibrillation	63 / 4	28 (43.8)	25 (39.1)	3 (4.7)	1 (1.6)	2 (3.2)
Pleural exudation	62 / 6	4 (6.5)	18 (29.0)	21 (33.9)	6 (9.7)	7 (11.3)
Pulmonary oedema	53 / 4	10 (18.9)	26 (49.1)	6 (11.3)	4 (7.5)	3 (5.7)
Pulmonary congestion	41					
Pulmonary oedema	12					
Respiratory failure	63 / 0	7 (11.1)	42 (66.7)	11 (17.5)	2 (3.2)	1 (1.6)
CPAP¤	24					
Failure to wean (>48h)	21					
Re-intubation	18					
Venous TEEΦ	6 / 0	0 (0,0)	1 (16.7)	2 (33.3)	0 (0.0)	3 (50.0)
Deep venous thrombosis	2					
Pulmonary embolus	4					
Arterial TEE	17 / 0	3 (17.6)	7 (41.2)	2 (11.8)	1 (5.9)	4 (23.5)
Acute myocardial infarction	9					
Stroke	4					
DIC*	3					
Arterial thrombosis	1					
Renal impairment	23 / 0	3 (13.0)	9 (39.1)	2 (8.7)	3 (13.0)	6 (26.1)
Renal failure	8					
Other renal	15					
Re-operation	79 / 0	4 (5.1)	37 (46.8)	25 (31.6)	6 (7.6)	7 (8.9)
Superficial wound rupture	9					
Deep wound rupture	37					
Anastomotic leakage	2					
Separation of stoma	1					
Re-perforation	6					
Peritonitis or abscess	2					
Post-operative obstruction	21					
Laparotomy pro haemostasis	1					
Death	91 / 0	19 (20.9)	9 (9.9)	14 (15.4)	15 (16.5)	34 (37.4)

¤ Continuous positive airway pressure. Φ Thrombo-embolic events. § Acute myocardial infarction. * Disseminated intravascular coagulation.

Table 4

Risk of a complication or all-cause mortality at 90 days and their association.

	Risk of a complication	Death (modified FTR§)	Crude analysis		Adjusted analysisθ	
	No. (%)	No. (%)	HR (95% CI)#	p	HR (95% CI)	p
Superficial wound complication	81 (24)	20 (25)	1.7 (1.0-2.9)	0.0393	1.6 (0.9-2.7)	0.1204
Deep wound complication*	45 (13)	16 (36)	2.5 (1.4-4.4)	0.0015	3.2 (1.7-5.8)	0.0001
Peritonitis	24 (7)	9 (38)	2.6 (1.3-5.4)	0.0067	-	-
Prolonged paralysis	145 (43)	30 (21)	1.1 (0.7-1.7)	0.8060	1.3 (0.8-2.2)	0.2872
Gastrointestinal bleeding	19 (6)	7 (37)	2.8 (1.3-6.2)	0.0084	-	-
Packed blood-products	47 (14)	21 (45)	3.1 (1.9-5.2)	<0.0001	1.7 (1.0-2.9)	0.0643
Pneumonia	110 (32)	40 (36)	3.4 (2.2-5.3)	<0.0001	2.4 (1.5-3.8)	0.0003
Urinary tract infection	44 (13)	11 (25)	2.0 (1.0-3.8)	0.0376	1.7 (0.8-3.4)	0.1494
Atrial fibrillation	63 (19)	33 (52)	4.4 (2.8-6.8)	<0.0001	3.3 (2.1-5.2)	<0.0001
Pleural exudation	62 (18)	26 (42)	3.9 (2.4-6.4)	<0.0001	2.3 (1.4-4.0)	0.0019
Pulmonary oedema	53 (16)	25 (47)	4.0 (2.5-6.4)	<0.0001	2.3 (1.4-3.8)	0.0011
Respiratory failure	63 (18)	29 (43)	3.9 (2.4-6.2)	<0.0001	2.9 (1.6-5.1)	0.0003
Venous TEEΦ	6 (2)	2 (33)	2.6 (0.6-10.6)	0.1840	-	-
Arterial TEEΦ	17 (5)	8 (47)	4.8 (2.3-9.9)	<0.0001	-	-
Renal impairment	23 (7)	13 (57)	6.8 (3.7-12.4)	<0.0001	-	-
Re-operation	79 (23)	25 (32)	2.4 (1.5-3.9)	0.0006	2.7 (1.6-4.5)	0.0001

§ Failure-to-rescue. # Hazard Ratio (95% Confidence interval). θ Variables adjusted for in the multivariable analysis: Hospital (Holbæk, Slagelse, and Køge), age, ASA class (categorised in class 1-2 or 3-5), pre-operative sepsis-2 score (categorised in group 0-2 or 3-4), cardiac co-morbidity (yes or no), hypertension (yes or no), renal co-morbidity (yes or no), active cancer (yes or no), the diagnosis (bowel obstruction or perforation), and the type of surgery (bowel resection and stoma formation or other procedures). *Analysed for laparotomies only, excluding 22 laparoscopic procedures. Φ Thrombo-embolic events. A p-value <0.003 is considered significant.

Table 5

The association between complications and 90-day mortality stratified on subgroups with gastrointestinal obstruction or perforation.

	Gastrointestinal obstruction				Gastrointestinal perforation			
			Crude analysis				Crude analysis	
	Risk of a complication, No. (%)	Death (FTR§), No. (%)	Hazard Ratio (95% CI#)	p	Risk of a complication, No. (%)	Death (FTR§), No. (%)	Hazard Ratio (95% CI#)	p
Superficial wound complication	56 (21)	10 (18)	1.2 (0.6-2.5)	0.5610	25 (28)	10 (40)	2.9 (1.2-7.0)	0.0173
Deep wound complication*	32 (12)	10 (31)	2.3 (1.1-4.7)	0.0193	13 (15)	6 (46)	2.5 (0.9-6.8)	0.0678
Peritonitis	11 (4)	6 (55)	4.7 (2.0-11.0)	0.0004	13 (15)	3 (23)	1.0 (0.3-3.3)	0.9740
Prolonged paralysis	103 (39)	18 (17)	1.0 (0.5-1.8)	0.9240	42 (48)	12 (29)	1.1 (0.5-2.6)	0.8590
GI¤ bleeding	13 (5)	5 (38)	3.3 (1.3-8.3)	0.0115	6 (7)	2 (33)	-	-
Packed blood-products	29 (11)	13 (45)	3.2 (1.7-6.1)	0.0002	18 (20)	8 (44)	2.6 (1.1-5.9)	0.0271
Pneumonia	75 (29)	27 (36)	3.9 (2.3-6.8)	<0.0001	35 (40)	13 (37)	2.3 (1.0-4.9)	0.0386
Urinary tract infection	35 (13)	10 (29)	2.5 (1.3-5.2)	0.0093	9 (10)	1 (11)	-	-
Atrial fibrillation	41 (16)	20 (49)	4.6 (2.6-7.9)	<0.0001	22 (25)	13 (59)	3.4 (1.7-6.8)	0.0008
Pleural exudation	34 (13)	15 (44)	4.5 (2.5-8.3)	<0.0001	28 (32)	11 (39)	2.7 (1.2-6.4)	0.0210
Pulmonary oedema	29 (11)	16 (55)	5.7 (3.2-10.3)	<0.0001	24 (27)	9 (38)	1.8 (0.8-4.2)	0.1410
Respiratory failure	41 (16)	18 (44)	5.2 (2.9-9.1)	<0.0001	27 (31)	11 (41)	2.1 (0.9-4.8)	0.0841
Venous TEEΦ	4 (2)	2 (50)	-	-	2 (2)	0 (0)	-	-
Arterial TEEΦ	10 (4)	5 (50)	4.8 (1.9-12.1)	0.0009	7 (8)	3 (43)	-	-
Renal impairment	17 (7)	10 (59)	9.5 (4.7-19.0)	<0.0001	6 (7)	3 (50)	-	-
Re-operation	55 (21)	16 (29)	2.6 (1.4-4.7)	0.0024	24 (27)	9 (38)	1.7 (0.7-4.0)	0.2050

§ Failure-to-rescue. # Confidence interval. ¤ Gastrointestinal θ *Analysed for laparotomies only, excluding 22 laparoscopic procedures. Φ Thrombo-embolic events. A p-value <0.003 is considered significant.

SUPPLEMENTARY MATERIAL (PAPER III)

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Supplementary table 1

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients with SUPERFICIAL WOUND COMPLICATION following emergency surgery for gastrointestinal obstruction or perforation.

	Patients with superficial wound complication	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	1.0 (0.6-1.6)	0.848
Køge	0.5 (0.3-0.9)	0.016
Age, years	1.1 (1.0-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.3)	0.370
Body mass index	1.0 (0.9-1.0)	0.102
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.273
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.4-1.5)	0.409
ASA Class 1-2	Ref	
Class 3-5	5.0 (3.0-8.1)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.1 (2.0-4.8)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.1-2.6)	0.015
Pulmonary comorbidity, No	Ref	
Yes	1.2 (0.7-2.1)	0.431
Hypertension, No	Ref	
Yes	1.5 (1.0-2.3)	0.049
Renal comorbidity, No	Ref	
Yes	2.8 (1.6-4.8)	<0.001
Diabetes, No	Ref	
Yes	1.0 (0.6-1.1)	0.987
Active cancer, No	Ref	
Yes	2.2 (1.4-3.4)	0.001
Laparoscopy	Ref	
Laparotomy	1.6 (0.6-4.3)	0.363
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.1 (1.3-3.1)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.2 (1.4-3.4)	0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.070
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.454
Time to surgery, hr	1.0 (0.9-1.0)	0.198
Time of surgery, hr	1.1 (0.9-1.3)	0.401

A p-value <0.05 is considered significant.

Supplementary table 2

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients with DEEP WOUND COMPLICATION following emergency surgery for gastrointestinal obstruction or perforation.

	Patients with deep wound complication (only including patients initially laparotomised)	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	1.1 (0.6-1.8)	0.843
Køge	0.6 (0.3-1.0)	0.040
Age, years	1.1 (1.1-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.2)	0.304
Body mass index	1.0 (0.9-1.0)	0.185
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.240
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.3-1.6)	0.401
ASA Class 1-2	Ref	
Class 3-5	4.9 (3.0-8.1)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.4 (2.1-5.4)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.1-2.6)	0.024
Pulmonary comorbidity, No	Ref	
Yes	1.2 (0.7-2.0)	0.615
Hypertension, No	Ref	
Yes	1.6 (1.0-2.4)	0.040
Renal comorbidity, No	Ref	
Yes	2.7 (1.5-4.7)	0.001
Diabetes, No	Ref	
Yes	1.0 (0.6-1.8)	0.980
Active cancer, No	Ref	
Yes	2.0 (1.2-3.2)	0.005
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.1 (1.4-3.3)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.2 (1.4-3.5)	0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.066
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.511
Time to surgery, hr	1.0 (0.9-1.0)	0.175
Time of surgery, hr	1.1 (0.9-1.2)	0.413

A p-value <0.05 is considered significant.

Supplementary table 3

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients with PROLONGED PARALYSIS following emergency surgery for gastrointestinal obstruction or perforation.

	Patients with prolonged paralysis	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	1.0 (0.6-1.6)	0.844
Køge	0.5 (0.3-0.9)	0.016
Age, years	1.1 (1.1-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.3)	0.374
Body mass index	1.0 (0.9-1.0)	0.107
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.273
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.4-1.5)	0.405
ASA Class 1-2	Ref	
Class 3-5	5.0 (3.0-8.1)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.1 (2.0-4.9)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.1-2.6)	0.015
Pulmonary comorbidity, No	Ref	
Yes	1.2 (0.7-2.1)	0.426
Hypertension, No	Ref	
Yes	1.5 (1.0-2.3)	0.049
Renal comorbidity, No	Ref	
Yes	2.8 (1.6-4.8)	<0.001
Diabetes, No	Ref	
Yes	1.0 (0.6-1.8)	0.971
Active cancer, No	Ref	
Yes	2.2 (1.4-3.5)	0.001
Laparoscopy	Ref	
Laparotomy	1.6 (0.6-4.3)	0.361
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.1 (1.3-3.1)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.2 (1.4-3.4)	0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.070
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.457
Time to surgery, hr	1.0 (0.9-1.0)	0.197
Time of surgery, hr	1.1 (0.9-1.3)	0.398

A p-value <0.05 is considered significant.

Supplementary table 4

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients receiving PACKED BLOOD-PRODUCTS following emergency surgery for gastrointestinal obstruction or perforation.

	Patients receiving packed blood products	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	0.9 (0.6-1.6)	0.817
Køge	0.5 (0.3-0.9)	0.015
Age, years	1.1 (1.1-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.3)	0.370
Body mass index	1.0 (0.9-1.0)	0.110
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.273
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.4-1.5)	0.404
ASA Class 1-2	Ref	
Class 3-5	4.9 (3.0-8.0)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.1 (1.9-4.8)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.0-2.6)	0.016
Pulmonary comorbidity, No	Ref	
Yes	1.2 (0.7-2.1)	0.428
Hypertension, No	Ref	
Yes	1.5 (1.0-2.3)	0.048
Renal comorbidity, No	Ref	
Yes	2.8 (1.6-4.8)	<0.001
Diabetes, No	Ref	
Yes	1.0 (0.6-1.8)	0.973
Active cancer, No	Ref	
Yes	2.2 (1.4-3.4)	0.001
Laparoscopy	Ref	
Laparotomy	1.6 (0.6-4.3)	0.366
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.0 (1.3-3.1)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.1 (1.4-3.4)	0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.080
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.489
Time to surgery, hr	1.0 (0.9-1.0)	0.197
Time of surgery, hr	1.1 (0.9-1.3)	0.404

A p-value <0.05 is considered significant.

Supplementary table 5

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients with PNEUMONIA following emergency surgery for gastrointestinal obstruction or perforation.

	Patients with pneumonia	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	1.0 (0.6-1.6)	0.836
Køge	0.5 (0.3-0.9)	0.016
Age, years	1.1 (1.1-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.3)	0.363
Body mass index	1.0 (0.9-1.0)	0.108
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.275
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.4-1.5)	0.390
ASA Class 1-2	Ref	
Class 3-5	4.9 (3.0-8.0)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.0 (1.9-4.8)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.1-2.6)	0.017
Pulmonary comorbidity, No	Ref	
Yes	1.2 (0.7-2.1)	0.433
Hypertension, No	Ref	
Yes	1.5 (1.0-2.3)	0.051
Renal comorbidity, No	Ref	
Yes	2.7 (1.6-4.8)	<0.001
Diabetes, No	Ref	
Yes	1.0 (0.6-1.8)	0.980
Active cancer, No	Ref	
Yes	2.2 (1.4-3.4)	0.001
Laparoscopy	Ref	
Laparotomy	1.6 (0.6-4.3)	0.364
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.1 (1.3-3.1)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.2 (1.4-3.4)	0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.074
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.462
Time to surgery, hr	1.0 (0.9-1.0)	0.203
Time of surgery, hr	1.1 (0.9-1.3)	0.399

A p-value <0.05 is considered significant.

Supplementary table 6

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients with URINARY TRACT INFECTION following emergency surgery for gastrointestinal obstruction or perforation.

	Patients with urinary tract infection	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	1.0 (0.6-1.6)	0.845
Køge	0.5 (0.3-0.9)	0.016
Age, years	1.1 (1.1-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.3)	0.376
Body mass index	1.0 (0.9-1.0)	0.105
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.275
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.4-1.5)	0.405
ASA Class 1-2	Ref	
Class 3-5	5.0 (3.1-8.1)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.1 (2.0-4.9)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.1-2.6)	0.015
Pulmonary comorbidity, No	Ref	
Yes	1.2 (0.7-2.1)	0.422
Hypertension, No	Ref	
Yes	1.5 (1.0-2.3)	0.050
Renal comorbidity, No	Ref	
Yes	2.8 (1.6-4.8)	<0.001
Diabetes, No	Ref	
Yes	1.0 (0.6-1.8)	0.978
Active cancer, No	Ref	
Yes	2.2 (1.4-3.4)	0.001
Laparoscopy	Ref	
Laparotomy	1.6 (0.6-4.3)	0.365
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.1 (1.3-3.1)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.2 (1.4-3.4)	0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.070
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.465
Time to surgery, hr	1.0 (0.9-1.0)	0.196
Time of surgery, hr	1.1 (0.9-1.3)	0.397

A p-value <0.05 is considered significant.

Supplementary table 7

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients with ATRIAL FIBRILLATION following emergency surgery for gastrointestinal obstruction or perforation.

	Patients with atrial fibrillation	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	1.0 (0.6-1.6)	0.863
Køge	0.5 (0.3-0.9)	0.017
Age, years	1.1 (1.1-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.3)	0.360
Body mass index	1.0 (0.9-1.0)	0.110
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.273
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.4-1.5)	0.404
ASA Class 1-2	Ref	
Class 3-5	4.9 (3.0-8.1)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.0 (1.9-4.8)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.1-2.6)	0.016
Pulmonary comorbidity, No	Ref	
Yes	1.3 (0.7-2.1)	0.430
Hypertension, No	Ref	
Yes	1.5 (1.0-2.3)	0.051
Renal comorbidity, No	Ref	
Yes	2.7 (1.6-4.8)	<0.001
Diabetes, No	Ref	
Yes	1.0 (0.6-1.8)	0.987
Active cancer, No	Ref	
Yes	2.2 (1.4-3.5)	0.001
Laparoscopy	Ref	
Laparotomy	1.6 (0.6-4.3)	0.369
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.0 (1.3-3.1)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.2 (1.4-3.4)	0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.073
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.462
Time to surgery, hr	1.0 (0.9-1.0)	0.203
Time of surgery, hr	1.1 (0.9-1.3)	0.402

A p-value <0.05 is considered significant.

Supplementary table 8

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients with PLEURAL EXUDATION following emergency surgery for gastrointestinal obstruction or perforation.

	Patients with pleural exudation	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	1.0 (0.6-1.6)	0.830
Køge	0.5 (0.3-0.9)	0.017
Age, years	1.1 (0.2-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.3)	0.382
Body mass index	1.0 (0.9-1.0)	0.109
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.272
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.4-1.5)	0.408
ASA Class 1-2	Ref	
Class 3-5	5.0 (3.0-8.1)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.1 (2.0-4.8)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.1-2.6)	0.016
Pulmonary comorbidity, No	Ref	
Yes	1.2 (0.7-2.1)	0.434
Hypertension, No	Ref	
Yes	1.5 (1.0-2.3)	0.050
Renal comorbidity, No	Ref	
Yes	2.8 (1.6-4.8)	<0.001
Diabetes, No	Ref	
Yes	1.0 (0.6-1.8)	0.971
Active cancer, No	Ref	
Yes	2.2 (1.4-3.4)	0.001
Laparoscopy	Ref	
Laparotomy	1.6 (0.6-4.4)	0.361
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.1 (1.3-3.1)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.2 (1.4-3.4)	0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.073
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.464
Time to surgery, hr	1.0 (0.9-1.0)	0.198
Time of surgery, hr	1.1 (0.9-1.3)	0.393

A p-value <0.05 is considered significant.

Supplementary table 9

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients with PULMONARY OEDEMA following emergency surgery for gastrointestinal obstruction or perforation.

	Patients with pulmonary congestion or oedema	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	1.0 (0.6-1.6)	0.830
Køge	0.5 (0.3-0.9)	0.016
Age, years	1.1 (1.0-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.3)	0.372
Body mass index	1.0 (0.9-1.0)	0.108
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.269
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.4-1.5)	0.403
ASA Class 1-2	Ref	
Class 3-5	4.9 (3.0-8.1)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.1 (2.0-4.8)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.1-2.6)	0.015
Pulmonary comorbidity, No	Ref	
Yes	1.2 (0.7-2.1)	0.443
Hypertension, No	Ref	
Yes	1.5 (1.0-2.3)	0.050
Renal comorbidity, No	Ref	
Yes	2.8 (1.6-4.8)	<0.001
Diabetes, No	Ref	
Yes	1.0 (0.6-1.8)	0.979
Active cancer, No	Ref	
Yes	2.2 (1.4-3.4)	0.001
Laparoscopy	Ref	
Laparotomy	1.6 (0.6-4.4)	0.360
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.0 (1.3-3.1)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.2 (1.4-3.4)	0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.077
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.462
Time to surgery, hr	1.0 (0.9-1.0)	0.200
Time of surgery, hr	1.1 (0.9-1.3)	0.404

A p-value <0.05 is considered significant.

Supplementary table 10

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients with RESPIRATORY FAILURE following emergency surgery for gastrointestinal obstruction or perforation.

	Patients with respiratory failure	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	1.0 (0.6-1.6)	0.840
Køge	0.5 (0.3-0.9)	0.017
Age, years	1.1 (1.1-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.3)	0.367
Body mass index	1.0 (0.9-1.0)	0.104
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.264
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.4-1.5)	0.393
ASA Class 1-2	Ref	
Class 3-5	4.9 (3.0-8.0)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.1 (2.0-4.8)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.1-2.6)	0.016
Pulmonary comorbidity, No	Ref	
Yes	1.2 (0.7-2.0)	0.451
Hypertension, No	Ref	
Yes	1.5 (1.0-2.3)	0.052
Renal comorbidity, No	Ref	
Yes	2.8 (1.6-4.8)	<0.001
Diabetes, No	Ref	
Yes	0.0 (0.0-0.0)	0.000
Active cancer, No	Ref	
Yes	0.0 (0.0-0.0)	0.000
Laparoscopy	Ref	
Laparotomy	1.6 (0.6-4.3)	0.364
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.0 (1.3-3.1)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.2 (1.4-3.4)	<0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.074
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.460
Time to surgery, hr	97.0 (0.9-1.0)	0.200
Time of surgery, hr	1.1 (0.9-1.3)	0.404

A p-value <0.05 is considered significant.

Supplementary table 11

The association between baseline variables and death in a uni-variable Cox regression model with delayed entry for patients with RE-OPERATION following emergency surgery for gastrointestinal obstruction or perforation.

	Patients having a re-operation	
Variable	Hazard ratio (95% confidence interval)	p value
Hospital, Holbæk	Ref	
Slagelse	1.0 (0.6-1.6)	0.840
Køge	0.5 (0.3-0.9)	0.016
Age, years	1.1 (1.1-1.1)	<0.001
Sex, Female	Ref	
Male	0.8 (0.5-1.3)	0.376
Body mass index	1.0 (0.9-1.0)	0.108
Tobacco use, No	Ref	
Yes	0.8 (0.5-1.2)	0.268
Excessive alcohol intake, No	Ref	
Yes	0.7 (0.4-1.5)	0.406
ASA Class 1-2	Ref	
Class 3-5	5.0 (3.1-8.1)	<0.001
Preoperative sepsis-2 score, 0-2	Ref	
3-4	3.1 (2.0-4.8)	<0.001
Cardiac comorbidity, No	Ref	
Yes	1.7 (1.1-2.6)	0.015
Pulmonary comorbidity, No	Ref	
Yes	1.2 (0.7-2.1)	0.429
Hypertension, No	Ref	
Yes	1.5 (1.0-2.3)	0.048
Renal comorbidity, No	Ref	
Yes	2.8 (1.6-4.8)	<0.001
Diabetes, No	Ref	
Yes	1.0 (0.6-1.8)	0.977
Active cancer, No	Ref	
Yes	2.2 (1.4-3.5)	0.001
Laparoscopy	Ref	
Laparotomy	1.6 (0.6-4.4)	0.359
Gastrointestinal obstruction	Ref	
Gastrointestinal perforation	2.0 (1.3-3.1)	0.001
Surgical procedure, Other	Ref	0.000
Bowel resection or stoma formation	2.2 (1.4-3.4)	0.001
Intraoperative fluid administration, mL	1.0 (1.0-1.0)	0.071
Intraoperative blood loss, mL	1.0 (1.0-1.0)	0.459
Time to surgery, hr	1.0 (0.9-1.0)	0.198
Time of surgery, hr	1.1 (0.9-1.3)	0.395

A p-value <0.05 is considered significant.

8.4 Paper IV

Goal-directed Fluid Therapy in Urgent Gastrointestinal Surgery – Study Protocol for a Randomised Multicentre Trial: The GAS-ART trial

BMJ Open

Goal-directed fluid therapy in urGent GAstrointestinal Surgery—study protocol for A Randomised multicentre Trial: The GAS-ART trial

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ABSTRACT

Introduction Intravenous fluid therapy during gastrointestinal surgery is a life-saving part of the perioperative care. Too little fluid may lead to hypovolaemia, decreased organ perfusion and circulatory shock. Excessive fluid administration increases postoperative complications, worsens pulmonary and cardiac function as well as the healing of surgical wounds. Intraoperative individualised goal-directed fluid therapy (GDT) and zero-balance therapy (weight adjusted) has shown to reduce postoperative complications in elective surgery, but studies in urgent gastrointestinal surgery are sparse. The aim of the trial is to test whether zero-balance GDT reduces postoperative mortality and major complications following urgent surgery for obstructive bowel disease or perforation of the gastrointestinal tract compared with a protocolled standard of care.

Methods/analysis This study is a multicentre, randomised controlled trial with planned inclusion of 310 patients. The randomisation procedure is stratified by hospital and by obstructive bowel disease and perforation of the gastrointestinal tract. Patients are allocated into either 'the standard group' or 'the zero-balance GDT group'. The latter receive intraoperative GDT (guided by a stroke volume algorithm) and postoperative zero-balance fluid therapy based on body weight and fluid charts. The protocolled treatment continues until free oral intake or the seventh postoperative day. The primary composite outcome is death, unplanned reoperations, life-threatening thromboembolic and bleeding complications, a need for mechanical ventilation or dialysis. Secondary outcomes are additional complications, length of hospital stay, length of stay in the intensive care unit, length of mechanical ventilation, readmissions and time to death. Follow-up is 90 days. We plan intention-to-treat analysis of the primary outcome.

Ethics and dissemination The Danish Scientific Ethics Committee approved the GAS-ART trial before patient enrolment (J: SJ-436). Enrolment of patients began in August 2015 and is proceeding. We expect to publish the GAS-ART results in Summer 2019.

Trial registration number EudraCT 2015-000563-14.

Strengths and limitations of this study

- This is a randomised controlled multicentre trial testing the effect of goal-directed fluid therapy in urgent gastrointestinal surgery.
- The multicentre design and an easy identification of the patient group supports broad clinical implementation of the study results.
- The primary outcome is clearly defined, clinically relevant and applies to the patients.
- Protocol adherence is secured by prelaminar and continuous teaching combined with regular assessment by the 'units of Good Clinical Practice', an independent data monitoring committee reinforcing the ICH-GCP (International Council for Harmonisation—Good Clinical Practice) guideline.
- Despite a set-up that is not blinded, the primary outcome will be assessor blinded.

INTRODUCTION

Death and complications are frequent following urgent major gastrointestinal surgery.[1] Mortality rates are 15% to 25%,[2–4] and the morbidity is ominous with complication rates reported for more than 50% of the patients.[5] Approximately 4500 patients annually undergo urgent gastrointestinal surgery in Denmark and several hundred of thousand people around the globe.[6 7] Intravenous fluid administration is a life-saving part of the perioperative treatment. The challenge is to determine the right volume of fluid to be given. Within planned gastrointestinal surgery, the fluid volume given has noticeably influenced the postoperative outcome.[8–13] However, trials testing perioperative fluid therapy for patients undergoing urgent surgery are sparse.

Intravenous fluid administration is necessary for upholding circulation and securing oxygen delivery to vital organs. Patients suffering from conditions requiring an urgent surgical intervention are frequently impaired by compromised fluid intake, nausea, vomiting, sepsis and other pathological fluid losses highlighting the vital

need for intravenous fluid therapy to prevent circulatory shock and death. Thus, liberal intravenous fluid administration in volumes far exceeding the losses before, during and after the surgical procedure is common practice.[14 15] On the other hand, there is no reason to believe that the harmful effect of fluid overload seen in studies of elective surgical patients is not valid for the patients undergoing urgent surgery. Interstitial oedema aggravate tissue inflammation, compromises wound healing and promotes anastomosis leakage.[8 10 16 17] In addition, cardiac arrhythmia, pulmonary oedema and acute respiratory distress syndrome may be the result.

The circulatory volume is difficult to measure or even estimate based on standard surveillance. Acute inflammation and stress response affect heart rate (HR) and diuresis. Arterial blood pressure and central vein pressure (CVP) may react on severe hypovolaemia, but does not reliably estimate normovolaemia or fluid overload, that is, does not tell when to stop the intravenous fluid infusion. Accordingly, the common physiological parameters are incapable of guiding clinical fluid therapy. As the patients are often hypovolaemic at admission, a simple in–out fluid balance (as used in trials of elective surgery to avoid fluid overload) is not useful for the urgent surgical patients.

The call for a more dynamic variable has led to the use of stroke volume (SV) to guide the fluid administration, the so-called goal-directed fluid therapy (GDT). Aiming at a submaximal SV using bolus infusions of a colloid, GDT possesses the ability to avoid both hypovolaemia as well as excessive fluid administration. Studies, using intraoperative GDT in planned gastrointestinal surgery, have shown to reduce length of hospital stay and complications.[12 13 18–21]

The presented trial is testing whether an intervention using intraoperative GDT followed by a postoperative zero balance, named the 'zero-balance GDT' strategy (the GDT group), reduces postoperative mortality and major complications following urgent surgery of obstructive bowel disease or gastrointestinal perforation compared with a standard group (SDT group). The STD group follows an algorithm for fluid therapy used in the PULP trial (Peptic ULcer Perforation)[22] resembling the fluid strategy used in River's study of patients with sepsis.[23] A fluid strategy, that to our knowledge is the best evidence-based fluid algorithm used in the urgent setting. This treatment is based on mean arterial pressure (MAP), diuresis, HR, CVP and central venous oxygen saturation ($S_{CV}0_2$). We suggest that zero-balance GDT may hold the ability to detect both hypovolaemia and fluid overload and guide the fluid therapy towards normovolaemia, thus reducing complications and death following urgent surgery.

The hypotheses are the following:

- Hypovolaemia as well as fluid overload compromises cardiac and pulmonary function prompting postoperative complications such as arrhythmia, myocardial infarcts, other thromboembolic events, pneumonia, pulmonary congestion, exudation in the pleural cavity, pulmonary oedema and acute respiratory distress syndrome.
- Hypovolaemia as well as fluid overload is harmful for the healing of tissues and surgical wounds, causing complications related to poor tissue healing and infection, that is, wound infections, wound rupture (superficial and deep), anastomosis leakage and separation of a stoma from the skin.

METHODS AND DESIGN

The trial is a randomised, parallel group, open-label, multicentre, superiority trial. The primary outcome will be assessor blinded. The study protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines.[24] We launched the study at five public university hospitals from the three most Eastern regions in Denmark handling urgent surgery from 1.5 million inhabitants. In Denmark, public hospitals are free of charge and treat all patients in the need for urgent surgery.

Eligibility criteria

Anaesthesiologists and surgeons collaborate to carry out the trial. Selected trial anaesthetists are responsible for conducting the intraoperative GDT intervention.

Inclusion criteria

- The need for urgent gastrointestinal surgery due to radiologically verified gastrointestinal perforation or obstructive bowel disease.
- The presence of an anaesthetist qualified of conducting the intraoperative GDT intervention.

Exclusion criteria

- Surgery of palliative purposes and the dying patient (American Society of Anaesthesiologist (ASA) group 5 to 6—ASA physical status classification).
- Major intra-abdominal surgery within the last 30 days.
- Iatrogenic gastrointestinal perforation.
- Dialysis on a regular basis.
- Patients unable to give informed consent for any reason.
- Age younger than 18 years.
- Pregnancy (positive urinary human chorionic gonadotropin).

Intervention

The patients are allocated to either (1) the GDT group or (2) the STD group. The treatment is initiated alongside the induction of the anaesthesia. Monitoring and data collection continue until the patient can drink and eat freely or to the seventh postoperative day.

In both groups, the treating physician administers preoperative antibiotics, antithrombotic and analgesia according to regional guidelines. The perioperative goals are MAP >65 mm Hg, HR <100 beats/min and SaO_2 (arterial oxygen saturation) >94%. Induction of anaesthesia is by propofol. Fentanyl and rocuronium are used if needed. Anaesthesia is by sevoflurane and fentanyl or propofol

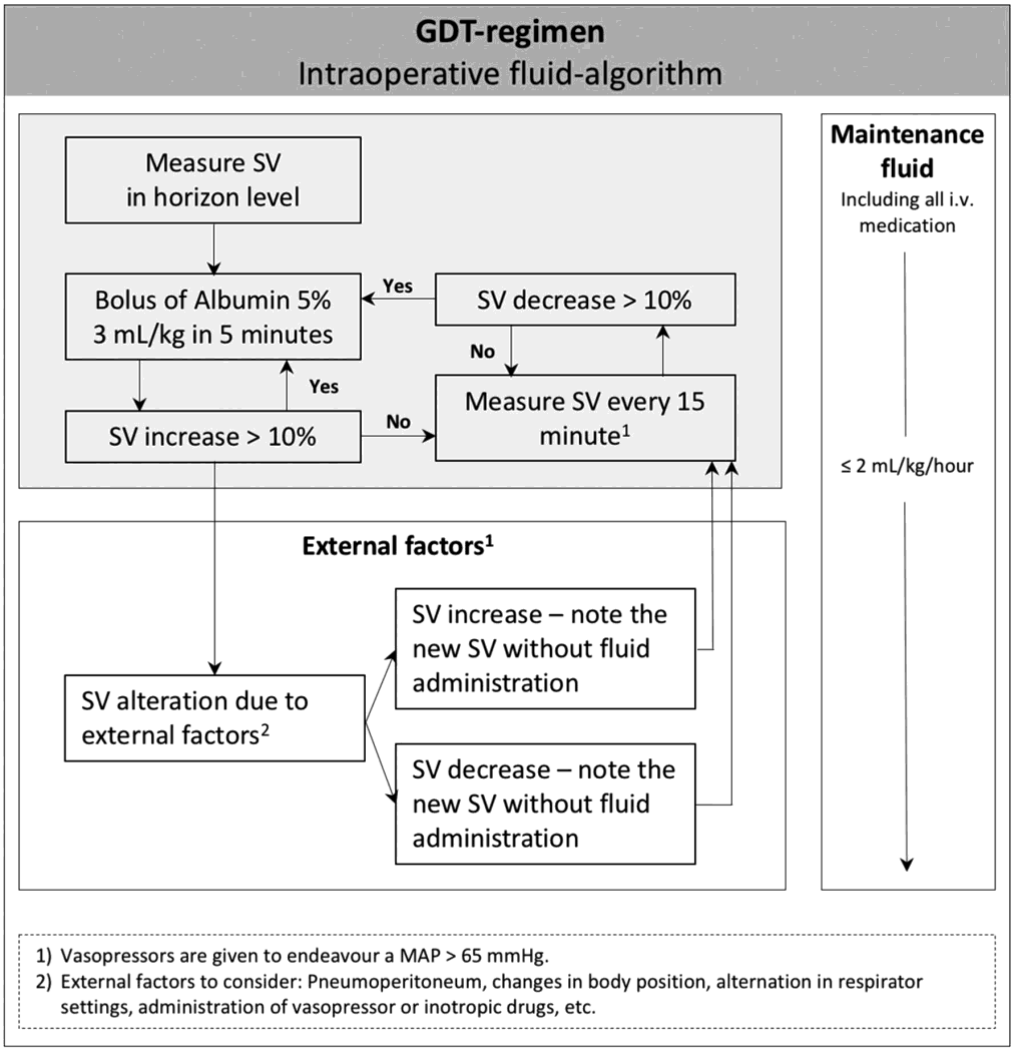

Figure 1 GDT regimen. Intraoperative fluid algorithm. GDT, goal-directed fluid therapy; i.v., intravenous; MAP, mean arterial pressure; SV, stroke volume.

and remifentanil. We allow local divergences. Additional epidural analgesia is used for laparotomy. We use invasive blood pressure monitoring in both groups and will keep haemoglobin >70 g/L (4.3 mmol/L) (or >80 g/L (5.0 mmol/L) for patients with chronic ischaemic heart disease and >90 g/L (5.6 mmol/L) in case of acute ischaemic heart disease) using blood replacement therapy. Critical blood loss is treated with replacement of blood, plasma and platelets in the ratio 3:3:1. Intraoperatively, hourly diuresis is registered and arterial blood samples analysed.

In the GDT group, fluid optimisation follows the SV algorithm seen in figure 1, which ends when the patient leaves the operating room and proceeds as zero-balance approach. We use the FloTrac sensor and the EV1000 monitor from Edwards Lifesciences. Before surgery, SV is measured and consecutive boluses of 3 mL/kg albumin 5% are given until increase in SV is below 10%. Then, SV is measured every 15 minutes. The procedure is repeated if SV decreases >10%. Changes in SV following external factors, such as pneumoperitoneum, changes in body position, alternation in respirator settings or administration of vasopressor or inotropic drugs, do not require fluid administration. Additional maintenance fluid replaces only pathological and physiological loses in the ratio 1:1, the latter amounting no more than 2 mL/kg/hour including all intravenous medication (antibiotics, anaesthetics, etc). The aim is a zero-balance, limiting unnecessary interstitial fluid accumulation. Additional vasopressors are given to endeavour a MAP >65 mm Hg.

Postoperative fluid administration is adjusted according to the fluid chart and the postoperative body weight as a zero-balance approach. Furosemide is given if the accumulated fluid balance exceeds 2 L or the body weight

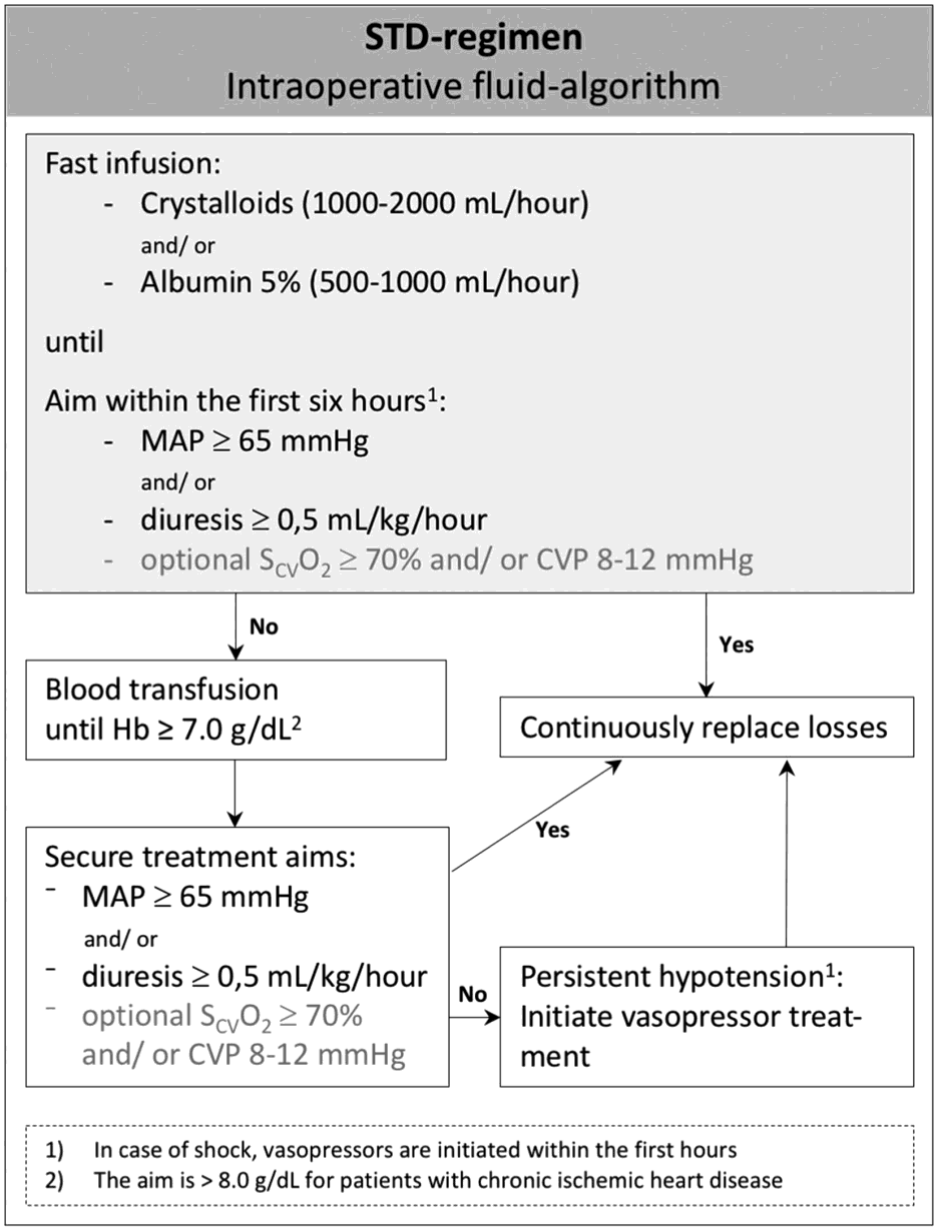

Figure 2 STD regimen. Intraoperative fluid algorithm. CVP, central vein pressure; Hb, haemoglobin; MAP, mean arterial pressure; $S_{CV}O_2$, central venous oxygen saturation; STD, standard group.

increases more than 2 kg. Prolonged intestinal paralysis might cause a net body weight gain of some kilograms and should not result in furosemide administration. Thus, clinical assessment alongside the data from fluid charts and body weight conditions the fluid replacement.

In the STD group, Ringers solution, saline 0.9% or albumin 5% are given intraoperatively to secure MAP >65 mm Hg and/or hourly diuresis >0.5 mL/kg/hour in accordance with the flowchart illustrated on figure 2. A central venous line is placed if the treating clinician finds it useful and CVP and $S_{CV}0_2$ used to guide the fluid therapy. Vasopressors are used only if persistent hypotension (MAP <65 mm Hg) occurs.

Postoperative fluid therapy is given according to local routines aiming at acceptable MAP >65 mm Hg, HR <100/min and diuresis >1 mL/kg/hour.

In both groups, postoperative analgesia is achieved with paracetamol, non-steroid anti-inflammatory drugs and/or opioids according to guidelines, besides epidural analgesia in case of laparotomy. Early mobilisation is endorsed by physiotherapist. Ventricular retention (failure to tolerate per oral intake) is treated with a gastric tube.

Metoclopramide or ondansetron is offered as antiemetic on demand.

The allocated treatment will be discontinued in all cases of a reoperation. The incidence will be registered as a part of the primary outcome. There is no other criteria for discontinuing the treatment in either group. Postoperative circulatory instability with a need for immediate care for example, septic shock is handled by the treating physician according to regional guidelines and overruling the allocated treatment. However, when the urgent phase has ended, the treatment returns to the allocated regimen and the episode is registered as an outcome.

Overall protocol adherence is secured by the project anaesthetist intraoperatively and postoperatively by the local investigator at the surgical ward. Individually training of selected trial physicians at the surgical and aesthetic wards was completed before study initiation at each involved hospital to secure protocol adherence. Formal presentation of the study was given to all staff at the intensive care unit, surgical and anaesthetic wards. Pocket cards with flowcharts were distributed. During the study period, continuous education is given to nurses and physicians in the teams responsible for the urgent surgical patients.

We use a detailed monitoring plan to evaluate protocol compliance. Regular reviewing of intraoperative and postoperative treating-related data at each hospital is conducted by the project leader as well as an independent data monitoring committee 'the unit of Good Clinical Practice', which assesses all phases of the GAS-ART trial. For example, intraoperatively one initial dose of human albumin and less than 2 mL/kg/hour of maintenance fluid is expected in the GDT group and infusion of more than 2000 mL crystalloids in the STD group. Monitoring reports are acquired on a regular basis throughout the entire study period. Areas with potential protocol deviations are corrected continuously.

Participant timeline

See figure 3 for the GAS-ART timeline.

Patient and public involvement

Patients or public were not involved in the development of the research question or outcome measures. Only medically trained physicians carry out the patient recruitment and management in the study. A trial physician gives written and oral information on positive and negative aspects of the intervention to the patient. Simultaneously, information on the final study results is offered to all participating patients on request.

OUTCOME MEASURES

All outcome measures are registered 30 days postsurgical. The primary outcome is registered 90 days postsurgical. Table 1 lists the outcome measures.

Primary composite outcome

- All-cause mortality
- Unplanned reoperations
  - Any unplanned laparotomy or laparoscopy
- Life-threatening bleeding complications
  - For example, cerebral haemorrhage, disseminated intravascular coagulation or other bleeding leading to medical, surgical or endoscopic intervention
- Life-threatening thromboembolic events
  - For example, acute myocardial infarction, stroke, pulmonary or intestinal emboli/thrombosis.
- Respiratory insufficiency
  - Demanding mechanical respiratory support including non-invasive ventilation
- Cardiac arrest (survived)
- Renal failure
  - Demanding dialysis

Secondary outcome measures

The secondary outcome measures are minor complications different from the primary composite outcome and specified time spans.

- Minor complications: A complication with a need for medical or surgical treatment.
- Timespan in the operating room, at the recovery room, at the intensive care unit, with mechanical respiratory support and until death.
- Postoperative days with dialysis.
- Length of hospital stay.

Sample size

Database inventory from Denmark shows a postoperative mortality rate of 15.7% after acute colonic surgery and one of 18.2% after operation for perforated ulcer.[4 25] The most ill patients are incapable of giving informed consent, thus excluded. However, the frequency of major complications is expected to be high in the population. We estimated the combined incidence of overall death and major complications to be 25%. A previous study testing a similar intervention in elective major gastrointestinal surgery has shown a risk reduction of 50%[8] and we estimated a reduction in the combined outcome to 12.5%. We accepted a 5% risk of type 1 error and a power to detect a reduction of 80%. The calculated sample size was 149 patients in each group. The variance is unlikely to follow a normal distribution and the number of patients needed was adjusted to 155 in each group—a total of 310 patients. We plan no interim analysis.

Recruitment

Teams of dedicated trial physicians at each hospital screen all adult patients with a need for urgent gastrointestinal surgery according to the eligibility criteria. Verbal and written study information is given prior to surgery by the surgeon or anaesthetist and written informed consent is obtained before randomisation. With a planned inclusion period of 2 to 3 years, we chose to initiate the trial in five hospitals. If the inclusion rate is unexpectedly low, additional physicians will be trained to perform the GDT intervention.

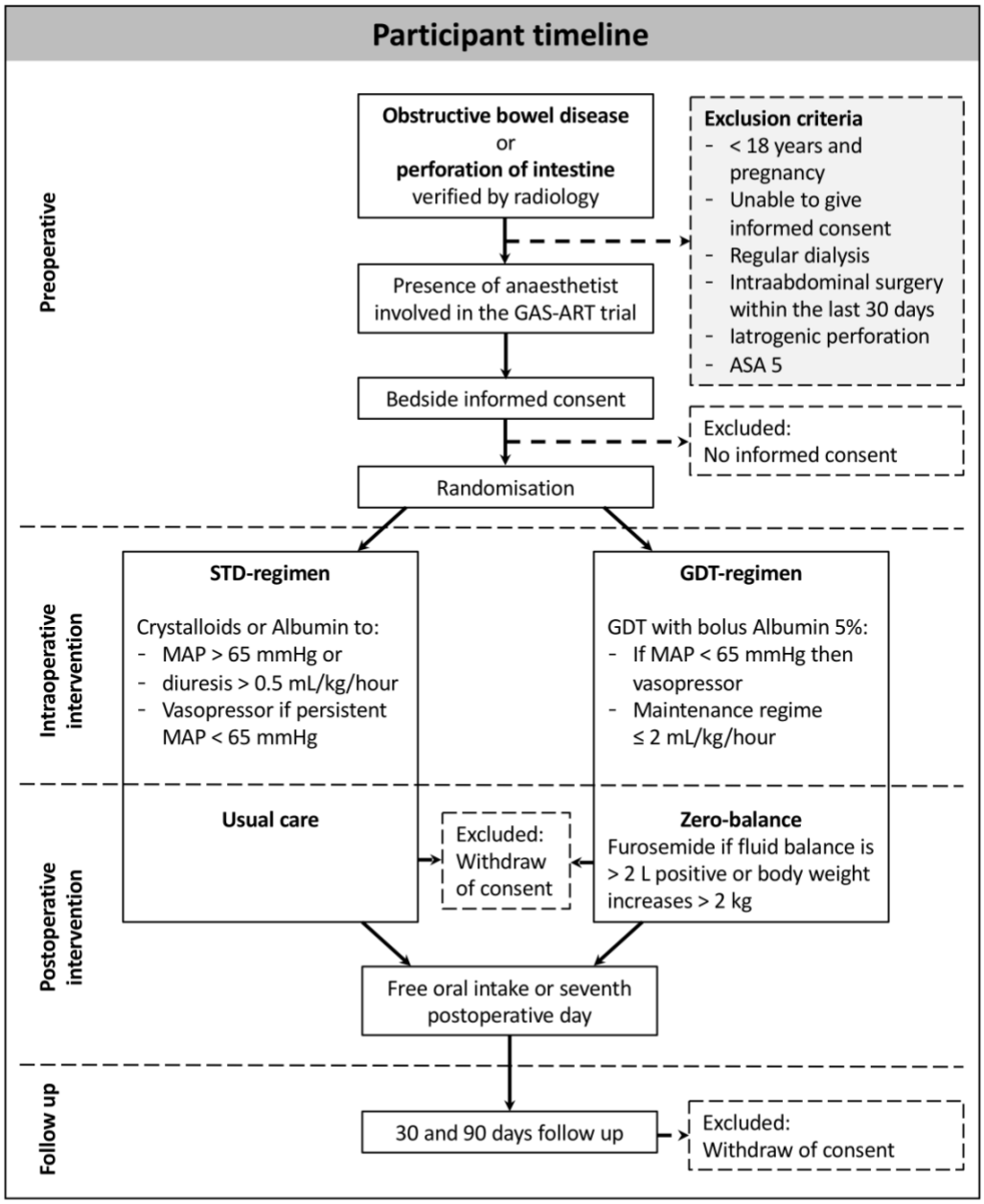

Figure 3 Participant timeline. ASA, American Society of Anaesthesiologists; GAS-AR T, GAstrointestinal Surgery Study protocol for A Randomised multicentre Trial; GDT, goal-directed f uid therapy; MAP, mean arterial pressure; STD, standard.

Table 1 Outcome measures

	Complication	Definition
Abdominal	Superficial wound rupture	Conservative or surgical treatment
	Superficial wound haematoma	Observed by a physician
	Superficial wound infection	Wound rupture, a need for removal of infected tissue or medical treatment
	Wound infection and fascial defect	A need for surgical cleavage or removal of infected tissue with fascial defect
	Facial rupture	Spontaneously fascial rupture
	Anastomosis leakage	Symptomatic and requiring treatment
	Separation of stoma	Cutaneous and subcutaneous defect
	Re-perforation	A need for relaparotomy
	Peritonitis	Debut intraoperatively or postoperatively
	Intra-abdominal abscess	Suspected radiologically with a need for medical or surgical treatment
	Obstructive bowel disease	A need for relaparotomy
	Prolonged paralysis of intestine	7 days without flatus or faeces
	Gastrointestinal bleeding	A need for surgical or endoscopic treatment
	Reoperation	Other unplanned intra-abdominal reoperations
Infectious	Sepsis	Worsening postoperatively, debut intraoperatively or postoperatively. Graded according to sepsis-2 definitions[43]
	Pneumonia	Radiological documentation and one clinical sign: fever, leucocytosis, coughing or crepitus
	Cystitis	Symptomatic and documented bacteriuria
	Other	With a need for medical or surgical intervention
Cardiopulmonic	Atrial arrhythmia	Verified by ECG and a need for treatment
	Ventricular arrhythmia	Verified by ECG and a need for treatment
	Acute myocardial infarction	ECG pathology and elevated cardiac enzymes
	Cardiac arrest	Diagnosed by a physician with or without successfully resuscitation
	Exudation to the pleural cavity	Verified by radiology
	Pulmonary congestion	Suspected clinically with bilateral crepitus and positive effect of diuretic treatment
	Pulmonary oedema	Radiographic suspicion and a need for intensive care
	Mechanical respiratory support	A need for intubation or continuous non-invasive ventilation
	Acute respiratory distress syndrome (ARDS)	ARDS according to the Berlin definition[44]
	Other	With a need for medical or surgical intervention
Thromboembolic	Pulmonary embolism	Verified by scintigraphy or CT scan
	Deep venous thrombosis	Verified by radiology
	Other	With a need for medical or surgical intervention
Renal	Renal failure	A need for dialysis
	Other	With a need for medical or surgical intervention
Central nervous system	Stroke or cerebral haemorrhage	Neurological symptoms and relevant radiology or diagnosed by neurologist
	Delirium/psychosis	Deficiency in orientation, level of consciousness, cognition and/or psychosis
	Other	With a need for medical or surgical intervention

ASSIGNMENT OF INTERVENTION

Allocation

We use a computer-generated block randomisation offered by OPEN-Randomise (Odense Patient data Explorative Network). We stratify by each hospital, and between obstructive bowel disease and perforation of the gastrointestinal tract. The study group of trial physicians is given access to OPEN-Randomise by username and password. The allocation sequence is concealed for all members of the study group. Trial physicians document the randomisation identifier number and allocation in the patient record and the case report form.

Blinding

The fluid therapy given in the GAS-ART trial includes the intraoperative and postoperative period at shifting departments involving many physicians and nurses. Additionally, clinical signs of hypovolaemia or hypervolaemia, for example, blood pressure, pulse, venous saturation, exudation to the pulmonic cavity, pulmonic oedema, subcutaneous oedema and diuresis are almost impossible to blind for the investigators. Thus, we could not find an effective way to blind the fluid therapy given in this trial. However, when the trial is completed, we conduct a blinded assessment of the primary outcome based on electronical patient records.

DATA COLLECTION, MANAGEMENT AND ANALYSIS

Intraoperative recording of fluid charts, blood pressure, HR and vasopressor use is collected by the trial physician. SV is recorded in the GDT group. In the postoperative phase, all enrolled patients are seen daily by a doctor on rounds who ensures protocol adherence. Data collection is in the electronical patient record, identified by the Danish personal registration number (CPR—det Centrale PersonRegister) including laboratory tests, radiology findings, microbiological results and other paraclinical results. Fluid charge and body weight are collected on paper forms. All patients will be Acute Physiology And Chronic Health Evaluation (APACHE II) scored the first day after surgery and patients admitted to the intensive care unit will be SOFA () scored daily. Follow-up is by the local investigator on postoperative days 30 and 90 either by telephone interview or by outpatient visit. Data transfer to the case report forms is secured only by the local investigator and trial physicians at each hospital to promote data quality and reviewed by the project leader. Additionally, registration of the primary outcome will be done by two independent and blinded accessors reading the patient records from all participating patients, blinded for information on the given fluid therapy, body weight measurements and allocation.

Case report forms and patient records will be stored at Holbaek Hospital in a secured locker. A database on the safe network of Holbaek Hospital is used for data entry securing confidentiality and allowing range checks for data validation. The steering committee will have access to the final trial dataset. Trial physicians can apply for access to the database. Local investigators will have access to trial data at their respective hospital.

Statistical methods and analysis

All data will be tested for normality and parametric statistics used for normal distributed data, otherwise non-parametric statistics are used. χ^2 test will be used for binominal data, Fischer's exact test when expected values are below 5. Risk will be calculated when relevant.

The primary composite outcome will be reported as 'intention to treat'. The result will be presented as an entity and separately for explorative reasons. If more than 20 patients are excluded after the randomisation, a 'per-protocol' analysis will be added. If baseline characteristics are skewed, the effect will be assessed using a multiple logistic regression model and the adjusted as well as the unadjusted analysis of the primary outcome will be presented. If more than 10% of the intraoperative data are missing, a worst-case and a best-case scenario will be presented. If the results are inconclusive, multiple imputations will be performed. Results will be presented two-tailed and a p-value<0.05 is considered significant.

The secondary outcomes will be analysed as 'intention to treat' and 'per protocol' if more than 20 patients are excluded after randomisation. Sequence for analysis is as follows: minor complications, specified time spans, physiological data and finally data from blood samples.

Subsequently, subgroup analysis of the hypothesis presented in the Introduction section will be done. We plan analysis by centre and type of operation (laparoscopic vs laparotomy) to detect potential differences between hospitals and the two treatments. The incidence and severity of sepsis is likely to differ between patients with gastrointestinal perforation or obstructive bowel disease and data analysed separately focusing on number of organ failures. The results will highlight trends for further investigation as the number of participants is inconsequential.

DATA MONITORING

The GAS-ART trial will be conducted in adherence to International Council for Harmonisation—Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki with data collection on paper case report forms. The GAS-ART trial is monitored by the independent units of Good Clinical Practice from Odense and Copenhagen securing an external monitoring of more than 10% of the completed case rapport forms and concordance with the ICH-GCP guidelines.

Four specified serious adverse reactions (SARs) as well as suspected unexpected serious adverse reactions (SUSARs) will be reported according to regulations from the unit of Good Clinical Practice and the Danish Health and Medicines Authority when suspected directly related to the infusion of saline, albumin or

Ringer's solution: acute anaphylactic reaction, hypernatraemia (s-Na >155 mmol/L), central pontine myelinolysis and seizures. The units hold the ability to abort the study if deemed necessary. The presence of SAR or SUSAR does not exclude the patient from the study since continuous fluid replacement therapy is unavoidable.

Patients withdrawing their consent are excluded from further intervention and data collection. Cases are expected to be few because the treatment and data collection rely on the healthcare professionals and deviation from usual practice is of little inconvenience for the patient. Patients withdrawing their consent will be replaced. Due to safety regulations, any observed SAR and SUSAR will be registered for all included patients.

ETHICS AND DISSEMINATION

The trial was approved by the Danish Scientific Ethics Committee and the Danish Data Protection Agency (REG-18–2015) before patient enrolment. The study is classified as a drug trial by the Danish Medicines Agency (2014 12 13 19). The trial is registered at the European Clinical Trials Database.

We identify no additional risk for the patients enrolled in the GAS-ART trial compared with usual practice. Arterial lines are generally used in patients with a need for urgent gastrointestinal surgery, and no additional invasive procedures will be applied.

Dissemination plan

We plan to publish study results in an international peer-reviewed journal. Negative as well as positive results will be published. Authors will have to meet the principles of the Vancouver Declaration.

The results will be presented at both national and international conferences of relevance. A letter will inform the participants about the study results when requested. Furthermore, the results will be presented at all involved hospitals and participating wards.

Trial status

Patient inclusion was initiated in August 2015 at Holbaek University Hospital. The additional four centres were consecutively introduced. By February 2016, the five planned centres had begun patient inclusion. We expect that patient inclusion will increase as study algorithms gradually become integrated in the daily routines at each centre. On 23 February 2018, 243 patients were included.

DISCUSSION

The GAS-ART trial is a randomised clinical trial testing the effect of two distinct fluid regimens on postoperative complications and death following urgent gastrointestinal surgery. Through the last 30 years, the effect of GDT optimisation has been tested on selected surgical patients, including high-risk patients. However, only a few studies have included emergency gastrointestinal surgical patients, and no trial has specifically targeted patients undergoing urgent surgery for obstructive bowel disease or gastrointestinal perforation.[26–30] Patients scheduled for urgent gastrointestinal surgery are often fluid deranged and preseptic at hospital admission, thus deviating markedly from the patients scheduled for planned surgery, and accordingly the mortality and complication rates are pronounced.[6 31] Studies of care bundles in emergency gastrointestinal surgery and meta-analysis suggest that high-risk surgical patients benefit from GDT optimisation.[32–34] The results has led to a widespread use of GDT algorithms within urgent gastrointestinal surgery. In opposition, a Cochrane review and a recent meta-analysis found no evidence to support this general implementation.[35 36]

The GAS-ART study is designed in accordance with a firm scientific structure and holds several strengths. The computer-generated block randomisation is blinded for all investigators, even the project leader. Furthermore, the units of Good Clinical Practice audits all patients enrolled in the trial and a list of all potential study patients, all together minimising the chance of allocation bias. The patient group is easily identified in daily clinical practice using standard radiological actions for the diagnosis combined with limited exclusion criteria favouring consecutivity of patient enrolment and lessening the chance of selection bias. The treatment in both the STD group and the GDT group was taught thoroughly to a selected group of trial physicians, responsible for the execution of the trial at each hospital. Additionally, continuously individual and formal teaching by one project leader secured unified implementation of both treatment regimens to lower performance bias. The primary outcome is clear, patient relevant and per-protocol defined consisting of six severe complications and death, and two previously randomised clinical trials emphasises their applicability.[8 37] The primary outcome markers demand medical or surgical treatment and will without exception be found in the patient's records. Therefore, we assume no missing data related to the primary outcome measures. Additionally, we plan a blinded assessment of the primary outcome to reduce detection bias. Data on fluid administration during surgery and at the postoperative care unit is routinely registered and we expect few missing data. Likewise, the secondary outcomes of minor complications call for treatment and few missing data are expected. In addition, the time periods of interest are all easily found in the patient journal.

The complexity of the study set-up, however, holds weaknesses that need to be addressed. The very nature of urgent surgery might impair enrolment of patients in the GAS-ART trial. First, operation should be performed as fast as possible, giving little time for information of the patient, little time for reflection and thus little time for informed consent. Second, the treating physicians and nurses focus on fast, often life-saving, treatment and stabilisation of the patient, which might compromise the time for study-related chores and limit patient enrolment.

Third, limiting patient enrolment to selected anaesthetists might be challenging because of working shifts. Blinding of investigators and patients was not doable under the given circumstances, holding a potential of performance bias. Emphasis on treatment optimisation might be applied to patients in the GDT group, potentially affecting the outcome not only related to the two different fluid regimens. On the other hand, the overall training and focus on intraoperative and postoperative fluid optimisation might enhance the general treatment and unify the care in the STD group and GDT group, thus eliminating a hypothetical positive effect of either fluid regimen. Finally, the use of a composite outcome holds a defiance. The most essential shortcoming of a composite outcome is the interpretation of the results. The difference between death and a severe complication is infinite in most situations, but not possible to distinguish in the result. However, the outcome parameters in the present trial will be reported both separately and as an entity.

The choice of intervention fluids needs to be addressed. GDT optimisation is usually based on consecutive infusion of hydroxyethyl starch entities. However, two recent studies showed increased need for renal replacement therapy and death using hydroxyethyl starch for fluid resuscitation in patients admitted at the intensive care unit. In addition, a Cochrane review questions the use of hydroxyethyl starch in randomised trials.[38–40] Use of crystalloids for GDT optimizations results in increased amounts of total intravenous fluid infusion.[41] The excessive infusion of chloride-containing fluids might cause hyperchloraemia which has been directly associated with increased 30-day mortality and length of hospital stay.[42] With an aim to avoid excessive fluid administration and due to the disputes about hydroxyethyl starch, we chose to use albumin for GDT optimisation in the GDT group. Additionally, the treatment algorithm in the STD group includes albumin for resuscitation and hinders a potential treatment bias.

The GAS-ART trial provides strong imperative results with a markedly clinical potential. Urgent gastrointestinal surgery is common and optimisation of the perioperative fluid regimens holds the potential to reduce postoperative death, complications and readmissions.

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Contributors BB: Developed the idea, searched the literature, drafted the protocol, conducted the power calculation, framed the intervention and the control treatment, planned the study, collected the data, planned the analysis and interpretation, revised and approved the final protocol. Raised the funds. AMM: Revised the intervention and the control treatment, planned the study, planned the analysis and interpretation, revised and approved the final protocol. AWV: Drafted the present manuscript, refined and revised the drafted protocol, registered the trial at EudraCT, obtaining legislative and ethical approvals, planned the study, revised the intervention, collected the data, revised the analysis and interpretation, revised and approved the final protocol. Responsible for initiating and conducting the trial. Raised the funds. AAA: Revised the drafted protocol, planned the study and intervention, collected the data, revised the analysis and interpretation, revised and approved the final protocol. Responsible for conducting and completion of the trial. Raised the funds. The steering committee consists of BB, AMM, AWV and AAA besides a local investigator from each participating hospital and is responsible for the inclusion and randomisation of patients, the protocol adherence, the data collection and the daily monitoring. The steering committee will critically read the final report and thereby have final authority over the report submitted for publication. The units of Good Clinical Practice monitor the trial at all centres participating.

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REFERENCES

1. Ingraham AM, Cohen ME, Bilimoria KY, *et al*. Comparison of 30-day outcomes after emergency general surgery procedures: potential for targeted improvement. *Surgery* 2010;148:217–38.
2. Saunders DI, Murray D, Pichel AC, *et al*. Variations in mortality after emergency laparotomy: the first report of the UK Emergency Laparotomy Network. *Br J Anaesth* 2012;109:368–75.
3. Barrow E, Anderson ID, Varley S, *et al*. Current UK practice in emergency laparotomy. *Ann R Coll Surg Engl* 2013;95:599–603.
4. Jørgensen HS. Danish Clinical Register of Emergency surgery for Peptic Ulcer. Danish Clinical Register of Emergency Surgery for Peptic Ulcer. Annual report 2015. *Akut Kir Database* 2016.
5. Vester-Andersen M, Waldau T, Wetterslev J, *et al*. Randomized multicentre feasibility trial of intermediate care versus standard ward care after emergency abdominal surgery (InCare trial). *Br J Surg* 2015;102:619–29.
6. Pearse RM, Harrison DA, James P, *et al*. Identification and characterisation of the high-risk surgical population in the United Kingdom. *Crit Care* 2006;10:R81.
7. Vester-Andersen M, Lundstrøm LH, Waldau T, *et al*. High mortality following emergency gastrointestinal surgery: a cohort study. *Eur J Anaesthesiol* 2013;30:4–5.
8. Brandstrup B, Tønnesen H, Beier-Holgersen R, *et al*. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003;238:641–8.
9. McArdle GT, McAuley DF, McKinley A, *et al*. Preliminary results of a prospective randomized trial of restrictive versus standard fluid regime in elective open abdominal aortic aneurysm repair. *Ann Surg* 2009;250:28–34.
10. Gao T, Li N, Zhang JJ, *et al*. Restricted intravenous fluid regimen reduces the rate of postoperative complications and alters immunological activity of elderly patients operated for abdominal cancer: a randomized prospective clinical trail. *World J Surg* 2012;36:993–1002.
11. Salzwedel C, Puig J, Carstens A, *et al*. Perioperative goal-directed hemodynamic therapy based on radial arterial pulse pressure variation and continuous cardiac index trending reduces postoperative complications after major abdominal surgery: a multi-center, prospective, randomized study. *Crit Care* 2013;17:R191.

12. Benes J, Chytra I, Altmann P, *et al*. Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of prospective randomized study. *Crit Care* 2010;14:R118.
13. Mayer J, Boldt J, Mengistu AM, *et al*. Goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized, controlled trial. *Crit Care* 2010;14:R18.
14. Bjerre CC, Holte K. [Perioperative fluid therapy in perforated ulcers]. *Ugeskr Laeger* 2009;171:1488–91.
15. Lilot M, Ehrenfeld JM, Lee C, *et al*. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. *Br J Anaesth* 2015;114:767–76.
16. Nisanevich V, Felsenstein I, Almogy G, *et al*. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005;103:25–32.
17. Piljic D, Petricevic M, Piljic D, *et al*. Restrictive versus standard fluid regimen in elective minilaparotomy abdominal aortic repair-prospective randomized controlled trial. *Thorac Cardiovasc Surg* 2016;64:296–303.
18. Noblett SE, Snowden CP, Shenton BK, *et al*. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg* 2006;93:1069–76.
19. Wakeling HG, McFall MR, Jenkins CS, *et al*. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth* 2005;95:634–42.
20. Phan TD, Ismail H, Heriot AG, *et al*. Improving perioperative outcomes: fluid optimization with the esophageal Doppler monitor, a metaanalysis and review. *J Am Coll Surg* 2008;207:935–41.
21. Rahbari NN, Zimmermann JB, Schmidt T, *et al*. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. *Br J Surg* 2009;96:331–41.
22. Møller MH, Adamsen S, Thomsen RW, *et al*. Multicentre trial of a perioperative protocol to reduce mortality in patients with peptic ulcer perforation. *Br J Surg* 2011;98:802–10.
23. Rivers E, Nguyen B, Havstad S, *et al*. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.
24. Chan AW, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200.
25. Jørgensen HS. on behalf of the Danish Akut kirurgi Database. Danish national database on colonorectal cancer. Annual repport 2014. 2014:01–182.
26. Shoemaker WC, Appel PL, Kram HB, *et al*. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988;94:1176–86.
27. Sandham JD, Hull RD, Brant RF, *et al*. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003;348:5–14.
28. Pearse R, Dawson D, Fawcett J, *et al*. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit Care* 2005;9:R687–93.
29. Pearse RM, Harrison DA, MacDonald N, *et al*. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA* 2014;311:2181–90.
30. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 1993;270:2699–707.
31. Ozdemir BA, Sinha S, Karthikesalingam A, *et al*. Mortality of emergency general surgical patients and associations with hospital structures and processes. *Br J Anaesth* 2016;116:54–62.
32. Dalfino L, Giglio MT, Puntillo F, *et al*. Haemodynamic goal-directed therapy and postoperative infections: earlier is better. A systematic review and meta-analysis. *Crit Care* 2011;15:R154.
33. Huddart S, Peden CJ, Swart M, *et al*. Use of a pathway quality improvement care bundle to reduce mortality after emergency laparotomy. *Br J Surg* 2015;102:57–66.
34. Tengberg LT, Bay-Nielsen M, Bisgaard T, *et al*. Multidisciplinary perioperative protocol in patients undergoing acute high-risk abdominal surgery. *Br J Surg* 2017;104:463–71.
35. Grocott MP, Dushianthan A, Hamilton MA, *et al*. Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery. *Cochrane Database Syst Rev* 2012;11:CD004082.
36. Rollins KE, Lobo DN. Intraoperative goal-directed fluid therapy in elective major abdominal surgery: a meta-analysis of randomized controlled trials. *Ann Surg* 2016;263:465–76.
37. Brandstrup B, Svendsen PE, Rasmussen M, *et al*. Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance? *Br J Anaesth* 2012;109:191–9.
38. Perner A, Haase N, Guttormsen AB, *et al*. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012;367:124–34.
39. Myburgh JA, Finfer S, Bellomo R, *et al*. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012;367:1901–11.
40. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2013:CD000567.
41. Yates DR, Davies SJ, Milner HE, *et al*. Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery. *Br J Anaesth* 2014;112:281–9.
42. McCluskey SA, Karkouti K, Wijeysundera D, *et al*. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. *Anesth Analg* 2013;117:412–21.
43. Levy MM, Fink MP, Marshall JC, *et al*. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31:1250–6.
44. Ranieri VM, Rubenfeld GD, Thompson BT, *et al*. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–33.