Acta Anaesth. Bel., 2023, 74 | Suppl. 1: *129-141*

Master thesis | Original study

Crystalloids vs. colloids during minimally invasive oesophagectomy and their influence on postoperative acute kidney injury, mortality, and morbidity: a retrospective observational study

P. Vandevelde[1], E. Hoste[2] , L. De Baerdemaeker[3]

[1]Department of Anesthesiology, Ghent University Hospital, Ghent, Belgium; [2]Department of Intensive Care Unit, Ghent University Hospital, Ghent Belgium; [3]Department of Anesthesiology, Ghent University Hospital, Ghent, Belgium.

Corresponding author: Dr. Vandevelde P., Ghent University Hospital, Department of Anesthesiology, Corneel Heymanslaan 10, 9000 Ghent, Belgium. E-mail: philipvandevelde1@gmail.com; Tel: 0032 495 77 15 35

Abstract

Background: **Open oesophagectomy is associated with significant morbidity and mortality. Minimally Invasive Oesophagectomy (MIE) is proven to be an effective less invasive alternative. Appropriate intravenous (I.V.) fluid therapy during this procedure remains a challenge. It remains unclear if colloids such as hydroxyethyl starch (HES) or gelatines are safe and efficacious for intraoperative use.**
Objectives: **In this study we examined if adding colloids to crystalloids intraoperatively had an effect on postoperative Acute Kidney Injury (AKI), mortality, and morbidity; when compared to using only crystalloids.**
Design and setting: **This retrospective observational study included 220 patients who underwent a MIE at the University Hospital of Ghent.**
Methods: **The usage of only crystalloids was compared with the usage of crystalloids and colloids (HES and/or gelatines). The primary outcome was AKI as defined by KDIGO criteria. Secondary outcomes were mortality (at 30 days, 90 days, and 1 year), length of stay (LOS) in the hospital, and the incidence of postoperative pneumonia.**
Results: **184 patients were administered only crystalloids, against 32 patients who were administered crystalloids and colloids (HES and/or gelatines). AKI occurred in only 2 patients (one in each fluid group), no further analyses was possible for this outcome. The estimated difference in 30-day, 90-day, and 1-year survival probability is 0.003 (95% CI: -0.003, 0.008), 0.012 (95% CI: -0.013, 0.037), and 0.04 (95% CI: -0.048, 0.129), respectively. There is thus a small, but non-significant, benefit of adding HES or gelatines during the operation. No significant effect was found for LOS or postoperative pneumonia.**
Conclusion: **The administration of intraoperative colloids (HES or gelatines) alongside with crystalloids during MIE, was not associated with an increase in the incidence of AKI, mortality, length of stay, or postoperative pneumonia, when compared with only crystalloids.**

Keywords: **Crystalloids, colloids, oesophagectomy, acute kindey injury (AKI).**

Introduction

Oesophagectomy is a high-risk surgical procedure associated with significant morbidity and mortality. Open oesophagectomy results in considerable trauma of access, generates a substantial systemic inflammatory response and is associated with significant postoperative pain and reduced postoperative mobilisation, resulting in significant impact upon quality of life[2,4,6].

Minimally invasive oesophagectomy (MIE) is shown to be as effective as open oesophagectomy and is associated with some beneficial outcomes such as less perioperative blood loss, reduced rate of pulmonary infections, a shorter hospital length of stay, and enhanced recovery and quality of life[2,4,6].

However, MIE brings with it specific anaesthetic challenges such as prolonged surgery, prolonged period of one lung ventilation, and difficulties with

This study was approved by The Ethics committee (EC) of University Ghent (Ugent) and Ghent University Hospital (UZ Gent), Corneel Heymanslaan 10, 9000 Ghent, Belgium - head of department Prof. Dr. Prof. dr. Renaat Peleman. The internal reference number of this study is THE-2023-0264 and approval took place on September 28 2023. .

assessment of fluid status and potential pulmonary complications of fluid overload[2,4,6].

There is a general consensus to restrict fluid administration during thoracic surgery to reduce acute lung injury and postoperative pulmonary complications. Conversely, inadequate intravascular volume may compromise tissue oxygenation, organ perfusion, and potentially increase the risk of anastomotic failure and leak. Appropriate fluid therapy should therefore be provided and current enhanced recovery after surgery (ERAS) guidelines recommend goal-directed fluid therapy (GDT) to maintain euvolemia[1,2,4-7]. Numerous studies have shown benefit of GDT by combining the use of fluids, ionotropes, and the use of measurements and indicators of cardiac output and stroke volume to improve blood flow intraoperatively to ultimately reduce mortality, morbidity and length of stay (LOS)[2,6,7,27,48,49].

Therefore, I.V. fluid therapy plays a vital role in establishing and maintaining cellular homeostasis perioperatively and in hospitalised patients. And while the correct use of fluids can be lifesaving, recent literature demonstrates that inappropriate fluid therapy can lead to significant morbidity and mortality. Ranging from inadequate resuscitation or rehydration leading to tissue hypoperfusion and hypoxia; to fluid overload, tissue oedema, organ damage and failure, electrolyte derangement, coagulation abnormalities, and increased need for transfusion. For these reasons, it has been recommended that the use of fluid therapy should be considered as medications in and of itself with specific indications, contra-indications and adverse effects. The type and dose of fluids for specific contexts and should be individualised to the patient rather than a 'one size fits all' approach[7,26,27].

Subsequently the optimal choice of fluids for peri-operative resuscitation remains unclear and has been an ongoing debate and point of controversy. Clinically, fluids can be categorised into crystalloids and colloids. Crystalloids, solutions containing small molecules (mainly electrolytes or glucose molecules) can further be divided into normal saline (NaCl 0,9%) and balanced crystalloids (such as Hartmann and Plasmalyte) and are thought to easily pass through capillary membranes expanding to extravascular space. Colloids, either synthetic such as hydroxyethyl starches (HES) or gelatines, or natural human albumin, contain macromolecules and are theoretically expected to remain intravascularly, due to their so called 'colloid oncotic pressure'. However, even though colloids may theoretically be more effective physiologically in reducing overall fluid amount and tissue oedema, numerous clinical trials have demonstrated that the difference in fluid balance achieved by use of colloids over crystalloids is generally fairly modest and often transient[1,22, 26,28,29,41].

These discrepancies have led to the development of a revised Starling model which incorporates the role of the endothelial glycocalyx in transcapillary fluid flow and plays a vital role in maintaining vascular integrity. This revised model could possibly explain why in systemic inflammatory states such as sepsis, burns, polytrauma, and surgery the integrity of the glycocalyx barrier is lost, inducing increased capillary permeability and fluid extravasation. Resulting in equivalent efficacy of resuscitation between crystalloids and colloids[26,28,29,32].

Moreover, in recent years a number of large RCTs in critically ill patients have demonstrated a higher mortality and incidence of acute kidney injury (AKI) and renal replacement therapy (RRT) with colloids compared with crystalloids, and more specifically associated with HES[26-29]. AKI in itself has been associated with a substantial increase in morbidity and mortality[20,47,54]. For instance, '6S' study found a higher mortality and RRT with HES vs Ringer's acetate in patients with severe sepsis[12]. Furthermore, in a subanalysis of the 'SAFE' study, there was a higher mortality in patients with traumatic brain injury (TBI) who were treated with albumin vs. saline[10]. Additionally, the 'CHEST' trial demonstrated an increase in RRT with HES vs. saline, and recommended that HES should be avoided in patients with severe sepsis or other critically ill patients at high risk for AKI[33]. The 'CRISTAL' trial however showed no difference in 28-day mortality, but lower 90-day mortality, more ventilator free and vasopressor-free days with colloids vs. crystalloids[15]. A 2018 systematic Cochrane review found no significant difference in mortality but increases in need for transfusion, RRT, and rash with HES vs. crystalloids[22]. In view of these findings, in 2013 both the FDA and European Medicines Agency issued warning against the use of HES in patients with critical illness, renal dysfunction, burns, or sepsis[28]. The use of HES has since then been under a lot of scrutiny.

However, it should be noted that these RCTs and subsequent warnings mainly concern a specific subgroup of ICU patients. The scientific evidence to guide fluid choice in the perioperative setting is limited and the findings and recommendations from septic and critically ill patients has been translated to the surgical patient without a clear rationale. While some have recommended avoiding perioperative HES, based in part on above mentioned critical care trials, others have argued that there is a role for the protocolized use of third generation HES or gelatines at lower doses and for shorter durations in selected

surgical patients. Most recently, the 'FLASH' trial, a large multicentre double-blind RCT compared 6% HES 130/0.4 with 0.9% saline in high-risk surgical patients using goal directed fluid therapy during and up to 24 after abdominal surgery. No significant difference in a composite outcome of death or major postoperative complications were found at 14 days. As such, these findings do not support the use of HES during surgery[18]. Additionally, most RCTs, reviews and meta-analyses on colloids vs. crystalloids do not demonstrate a benefit with a suggestion of harm[29,35,36,40-42,45,48].

Some notable exceptions in favour of colloids are a 2018 RCT comparing HES with Plasmalyte in an intraoperative goal directed fluid therapy using a closed loop system, which suggested fewer postoperative complications with colloid-based goal-directed fluid therapy, possibly related to a lower intraoperative fluid balance[23]. Additionally, a 2021 systematic review and meta-analysis researching the safety and efficacy of HES in surgery and trauma, suggested that HES are safe and efficacious in the perioperative setting, and that with adequate indication, a combination of crystalloids and volume replacement with HES might have a clinically beneficial effect over using only crystalloids, with a reduced need for vasopressors and decreased length of hospital stay[25]. Lastly, a 2017 review of perioperative choice of fluid type, suggested that restoration of intravascular volume after acute hypovolemia might be more effective using colloids, and that colloids might have a restorative capacity for the endothelial glycocalyx and microcirculatory function[29].

Thus, the literature on the debate between colloids and crystalloids remains inconclusive.

In this retrospective study, we observed if the choice of perioperative fluid (colloids vs crystalloids) during MIE, had any impact on postoperative mortality, morbidity, and AKI.

Methods

This study utilized data from a large surgical data base of patients undergoing an oesophagectomy at the University Hospital of Ghent. This study was approved by The Ethics committee (EC) of University Ghent (Ugent) and Ghent University Hospital (UZ Gent), Corneel Heymanslaan 10, 9000 Ghent, Belgium - head of department Prof. Dr. Prof. dr. Renaat Peleman. The internal reference number of this study is THE-2023-0264 and approval took place on September 28 2023. The requirement for obtaining patient consent was waived because the study utilized only previously collected data.

All surgical patients who underwent a minimally invasive oesophagectomy (MIE) between October 2015 and December 2021 at the University Hospital of Ghent were included. General patient demographic data was acquired from the preoperative consultation. Surgical data and specific cancer related data was provided from the surgical department. Perioperative data was collected from anaesthesiology charts. Lastly, postoperative data and laboratory results were collected from the ICU and surgical hospitalisation. Long term follow-up data collection was acquired either from surgical follow-up in hospital or from the national medical data accessing portal COZO. All data was reviewed and validated by anaesthesiology residents. In total, 220 patients were included.

All patients were administered crystalloids. A comparison of only crystalloids vs only gelatines and/or HES is thus not possible. However, we can still contrast administering gelatines and/or HES with not administering them. Furthermore only 7 and 25 patients were administered gelatines and HES, respectively. This will probably not suffice to detect a treatment effect, if present. To (slightly) increase the power, we looked at the effect of receiving gelatines or HES. Thus, fluid therapy was categorized as either only crystalloids or crystalloids and colloids (HES and/or gelatines). The crystalloids used were normal saline (NaCl 0,9%), Hartmann, and Plasmalyte. The HES used was Volulyte (6% HES 130/0.4 in a balanced electrolyte solution), and the gelatin used was Geloplasma (a modified balanced fluid gelatin).

Intraoperatively, fluid administration was carefully managed. Fluid overload was avoided to minimize the risk of potential pulmonary oedema associated with surgical manipulation of the lungs. A central venous pressure (CVP) goal was set between 5 – 10 mmHg, diuresis was maintained above 0.5 ml.kg-1.hr-1, and baseline fluid administration was set at ± 3.5 ml.kg-1.hr-1 to maintain left ventricular end diastolic volume index (LVEDI) and cardiac index (CI), as suggested by Concha et al. for laparoscopic surgery[57]. Fluid losses on top of baseline fluid administration were compensated. Low dose furosemide (2.5 – 5 mg) was considered in case of oliguria despite of abovementioned fluid management.

The primary outcome was the incidence of postoperative AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition[9]. AKI was defined as any of the following outcomes: increase of serum creatinine ≥ 0,3 mg/dl within 48h or ≥ 50% within 7 days.

The secondary outcomes included mortality, both at 30 days, 90 days and 1-year survival; and morbidity outcomes were defined as length of

stay (LOS) in the hospital, and the incidence of postoperative pneumonia.

For statistical analysis the program R was used. For time-to-event outcomes (survival and LOS), a Kaplan-Meier analysis was used to estimate the outcomes. To control for baseline variables, a Cox proportional hazard (PH) model was used since it requires the fewest assumptions. The main problem with a Cox PH model is the interpretation. In this analysis the effect of the variables on survival and LOS are summarized in a hazard ratio model. This reveals a positive or negative effect, but is difficult to interpret the size of the effect. To overcome this, the estimated survival was evaluated with a counterfactual survival function (or regression standardization) for the Cox PH model. For binary outcomes such as pneumonia, a logistic regression model was used. The effect of such a model is expressed in odds ratios. No further regression standardization was needed. Some pragmatic choices in the statistical analysis were needed to increase the power of the analysis. These are further explained alongside the results.

Results

General Data Exploration

We start with a very general data exploration to gain some insights into the data. The following Table I summarizes all important variables. For continuous variables, the median and quartiles are given. P-values for the comparison of crystalloids with crystalloids + gelatines or HES are also given. These p-values are merely exploratory and should not be interpreted too much.

A few comments are in place after looking at this table:

For some variables, there is a considerable amount of missing data. In principle, specialized methods are available to deal with this. However, this is already quite advanced and outside the scope of the current analysis. Therefore, an available case (AC) will be used further on. AC means that observations with missing values are ignored if the missing value is required for the analysis. If a patient has a missing value in a variable that is not used in a particular analysis method, then this patient is still used for the analysis. The power of an AC analysis decreases considerably if a variable with many missing values is used. Therefore, the following variables with too many missing values will not be used: Body Mass Index (BMI), estimated glomerular filtration rate preoperative (eGRF preop), and Coronary Heart Disease.

This is a rather pragmatic choice. Indeed, these variables could be important. Nonetheless, including these variables would mean that the effective sample size decreases significantly, which results in decreased power.

Some binary baseline variables have a very unbalanced distribution, i.e., categories with only few patients. These are not further used because they are not very informative and could lead to instability in estimation of the models: Chronic Obstructive Pulmonary Disease (COPD) and liver disease.

The following variables will be "controlled for" in all subsequent analyses. If these variables are sufficient to control confounding, then the resulting treatment effect estimates can be given a causal interpretation. However, unmeasured confounding variables are very likely. Hence, one should be careful with causal interpretations. Even more so because this is retrospective data. These variables are: Diabetes Mellitus (DM), Arterial Hypertennsion (AHT), Preoperative Creatine (creat preop), Preoperative Hemoglobin (Hb preop), Total Duration, Lymph Nodes Staging, Total Amount of Crystalloids.

AKI

Only 2 patients fit the definition of AKI. One in each fluid group, both KDIGO Stage 1. Further analyses are not possible with only 2 cases. Thus, no significant difference was detected.

Mortality

In this section, the survival outcomes are analyzed. We start with an exploration of the survival data. Next, a Cox proportional hazards (PH) model is fitted taking into account possible confounding variables. From this Cox PH model, the 1-year survival probabilities for the different treatment groups are computed together with estimates of uncertainty (standard errors and confidence intervals).

Data Exploration

In survival analysis, the most basic analysis is the Kaplan-Meier (KM) survival function. This is a non-parametric method to estimate the survival function, possibly stratified by categorical variables. In this context, "non-parametric" means that this analysis does not rely on any assumptions, except independent censoring. The latter signifies that censoring should be independent of the actual survival time. This is actually assumed in every survival analysis, but can often be justified. In these data, censoring is mostly "at random", i.e., not related to the survival time itself.

The overall KM estimate of the survival function is shown in the next plot (Figure 1) together with a 95% confidence interval (CI).

Table I. — General Data exploration.

Characteristic	Only Crystalloids, N = 184	Crystalloids + HES or Gelatines, N = 32	p-value
Sex			0.7
Man	150 (82%)	27 (84%)	
Woman	34 (18%)	5 (16%)	
COPD	19 (10%)	6 (19%)	0.2
AHT	73 (40%)	17 (53%)	0.2
BMI	25.1 (22.8, 28.5)	25.8 (23.4, 28.0)	0.8
Unknown	30	4	
DM	30 (16%)	3 (9.4%)	0.4
Liver Disease	9 (4.9%)	0 (0%)	0.4
Coronary Heart Disease	26 (15%)	2 (6.5%)	0.3
Lymph Nodes Staging (N)			0.6
0	102 (56%)	15 (47%)	
1	52 (28%)	12 (38%)	
2	21 (11%)	3 (9.4%)	
3	8 (4.4%)	2 (6.3%)	
Total duration (min)	498 (444, 546)	513 (458, 568)	0.4
Duration abdominal (min.)	200 (180, 240)	210 (161, 240)	0.6
Unknown	9	0	
Duration thoracic (min.)	195 (180, 240)	198 (164, 229)	0.4
Unknown	9	0	
Crystalloids (n)	182 (100%)	32 (100%)	
Unknown	2	0	
HES	0 (0%)	25 (78%)	<0.001
Gelatines	0 (0%)	7 (22%)	<0.001
Total Crystalloids (ml)	3,500 (2,700, 4,000)	3,500 (2,500, 5,000)	0.5
Unknown	2	0	
Hartmann (ml)	2,500 (1,000, 3,000)	2,750 (2,000, 3,625)	0.035
Unknown	2	0	
Plasmalyte (ml)	0 (0, 1,000)	0 (0, 0)	0.015
Unknown	2	0	
NaCl 0.9% (ml)			0.5
0	12 (6.6%)	0 (0%)	
500	158 (87%)	29 (91%)	
1000	9 (4.9%)	3 (9.4%)	
1500	2 (1.1%)	0 (0%)	
2000	1 (0.5%)	0 (0%)	
Unknown	2	0	
Volulyte (ml)			<0.001
0	184 (100%)	7 (22%)	
500	0 (0%)	19 (59%)	
1000	0 (0%)	6 (19%)	
Hb preop	12.85 (11.53, 13.90)	12.70 (11.58, 13.98)	0.8
Unknown	2	0	
eGFR preop	73 (58, 79)	68 (58, 85)	0.7
Unknown	123	22	
Creat preop (mg/dl)	0.87 (0.72, 1.02)	0.80 (0.73, 1.01)	0.6
Unknown	2	1	
Creat day 1 postop	0.76 (0.66, 0.91)	0.71 (0.62, 0.84)	0.3
Max. creat day 2-7	0.72 (0.63, 0.82)	0.69 (0.60, 0.85)	0.5
LOS ICU (days)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	>0.9
Unknown	16	0	
LOS hospital (days)	14 (11, 20)	14 (12, 21)	0.7
Unknown	1	0	
Pneumonia	56 (30%)	10 (31%)	>0.9
Mortality	71 (39%)	11 (34%)	0,7
Survival time (days)	718 (306, 1,201)	826 (389, 1,681)	0.3
Unknown	4	2	

COPD = Chronic Obstructive Pulmonary Disease, AHT = Arterial Hypertension, BMI = Body Mass Index, DM = Diabetes Mellitus, Hb = hemoglobin, eGFR = Estimated Glomerular Filtration Rate, Creat = creatinine. Preop = preoperative, Postop = postoperative, LOS = length of stay, ICU = Intensive Care Unit.

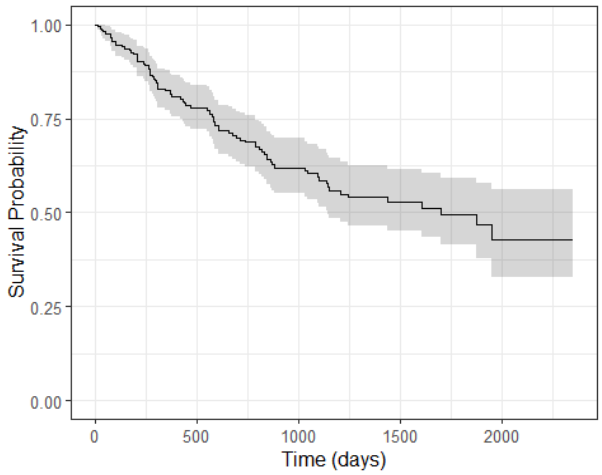

Fig. 1 — Overall KM estimate of survival function with 95% CI.

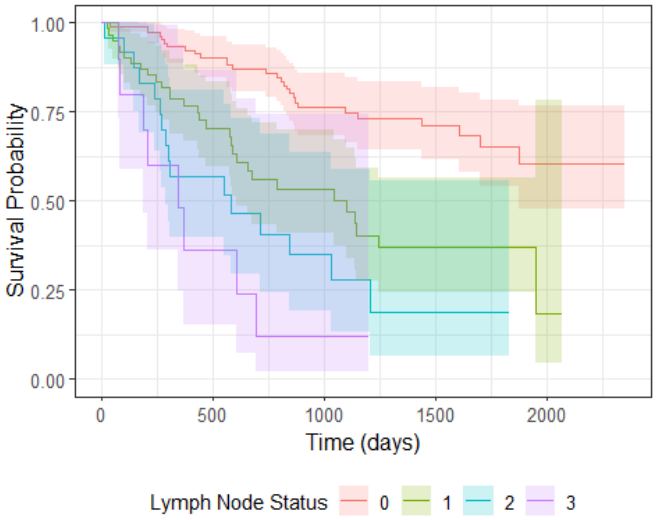

Fig. 2 — KM estimate of the survival function, stratified by Lymph Node Status with 95% CI.

The KM estimate of the survival function, stratified by Lymph Node Status, is given in the next plot (Figure 2). Lymph Node Status clearly is a very strong prognostic factor.

In the next 3 plots, the KM estimate of the survival function is stratified by different categorical variables (Figure 3). These plots do reveal some patterns, but not as outspoken as for lymph node status.

Cox PH Model

A Cox proportional hazards model is fitted controlling for the variables mentioned before. Because the causal effect of crystalloids only versus crystalloids and HES or gelatin is of interest, the corresponding variable is also added to the survival model. The estimated model is summarized in the next table (Table II).

Looking at the p-values in this model, only two variables are significant at the 5% level of significance:

Hb Preop: The estimated hazard ratio for a one-unit increase in Hb Preop is 0.841 (95% CI: 0.724, 0.976). This is in line with intuition. The p-value is 0.023.

Lymph Node Status: The estimated hazard ratio for a one-stage increase is 2.022 (95% CI: 1.595, 2.565). This is in line with intuition. The p-value is < 0.001.

The main interest is not in the effect of baseline covariates, but in the effect of the type of fluids on 30-day, 90-day, and 1-year survival. From the estimated Cox PH model, we compute this treatment effect next. Note that this treatment effect on the hazard scale was not significant. Therefore, the treatment effect will also not be significant on the 30-day, 90-day, and 1-year survival scale.

In the next plots, two estimated survival functions are compared (Figure 4). These are two so-called counterfactual survival functions. They correspond to the survival function "had everyone received only crystalloids" and "had everyone

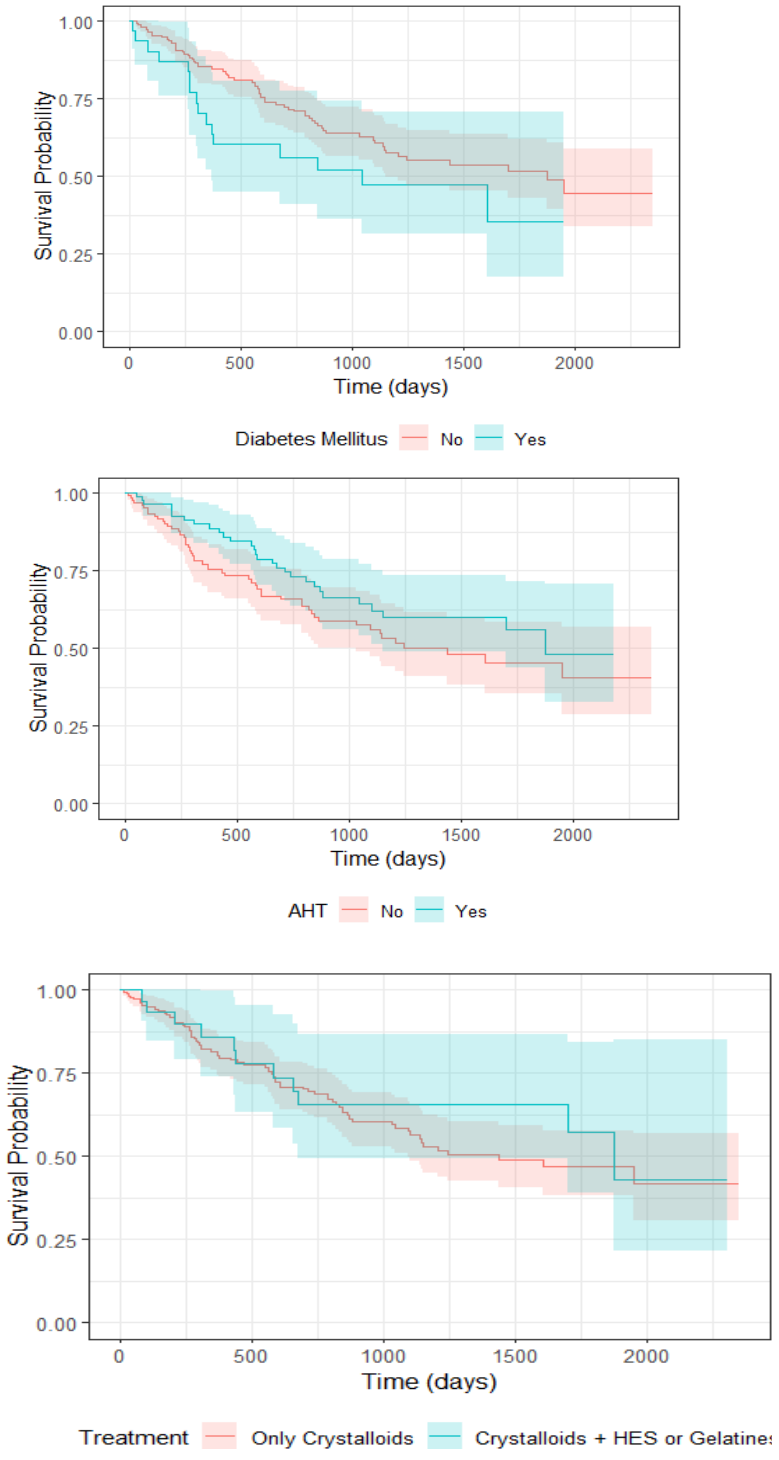

Fig. 3 — KM estimate of survival function, stratified by DM (3A), AHT (3B), and choice of fluid (only crystalloids vs crystalloids and colloids) (3C). Shown with 95% CI.

received crystalloids and HES or gelatin". The dashed lines are the corresponding pointwise 95% confidence intervals. The confidence interval for the survival function "had everyone received crystalloids and HES or gelatin" is very wide. This is a consequence of having only 32 patients in this group.

The test for a treatment effect on 30-day, 90-day, and 1-year survival was calculated. The estimated difference in 30-day survival probability is 0.003 (95% CI: -0.003, 0.008). The estimated difference in 90-day survival probability is 0.012 (95% CI: -0.013, 0.037). The estimated difference in 1-year survival probability is 0.04 (95% CI: -0.048, 0.129). There is thus a small, but non-significant, benefit of adding HES or gelatines during the operation. As stressed before, this treatment effect can only be interpreted as causal if we have controlled for all confounding variables.

Table II. — COX PH model mortality.

Characteristic	HR	95% CI	p-value
DM			
No	—	—	
Yes	1.15	0.64, 2.09	0.6
AHT			
No	—	—	
Yes	0.83	0.51, 1.34	0.4
Creat preop	1.32	0.70, 2.49	0.4
Hb preop	0.84	0.72, 0.98	0.023
Total duration	1.00	1.00, 1.01	0.075
Lymph Nodes Status	2.02	1.59, 2.56	<0.001
Total Crystalloids	1.00	1.00, 1.00	0.4
HES or Gelatines	0.74	0.38, 1.42	0.4
HR = hazard ratio, CI = Confidence Interval.			

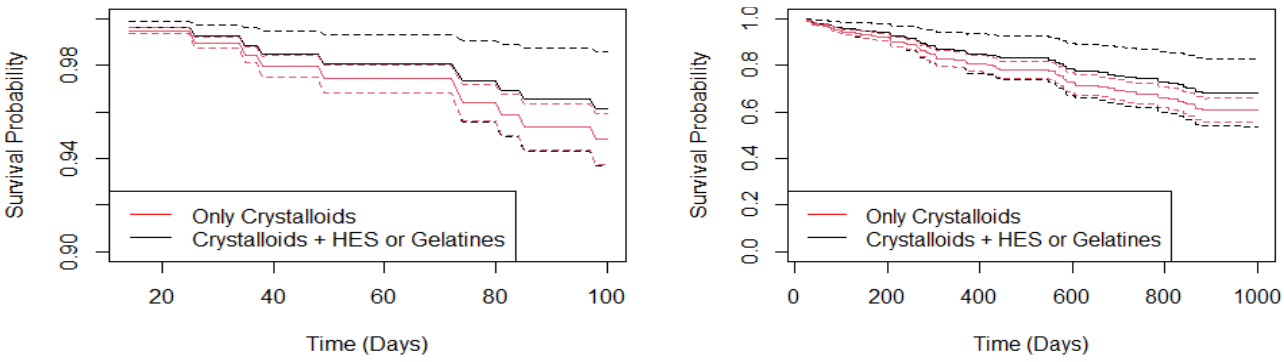

Fig. 4 — Counterfactual survival functions with 95% CI.

Morbidity

Length of stay

Data exploration

The same exploratory KM plots as for survival are given next (Figure 5). The only difference is that the survival as outcome is replaced with length of stay in hospital.

COX PH Model

The same type of analysis is performed as in the previous section, but now replacing time-to-death with length of stay in hospital as outcome variable. A Cox proportional hazards model is fitted controlling for the variables mentioned before. Because the causal effect of crystalloids only versus crystalloids and HES or gelatines is of interest, the corresponding variable is also added to the survival model. The estimated model is summarized in the next table (Table III).

Looking at the p-values in this model, only one variable is significant at the 5% level of significance: AHT: The estimated hazard ratio for AHT present versus absent increase in AHT is 0.719 (95% CI: 0.537, 0.964). The p-value is 0.027. The estimated hazard ratio is smaller than one. This means that AHT present decreases the probability of the event, i.e., decreases the probability of being discharged from hospital. So, in this setting, it decreases the probability of a positive outcome. In the previous analyses, it is the other way around. Death is a negative outcome. Indeed, with death as outcome, a hazard ratio smaller than 1 indicates a clinically positive effect.

The p-value for the treatment effect of the type of fluid is 0.718. There is thus no significant effect of the type of fluid on the length of stay. The same comparison of counterfactual survival functions is given next in Figure 6. These are often much easier to interpret than a single p-value in a Cox PH model.

The two estimated survival functions almost perfectly overlap. Indicating that there is no evidence for an effect of the type of fluid on the length of stay.

Pneumonia

A logistic regression model is fitted with pneumonia as binary outcome variable and the same variables as before as covariates. The estimated model is summarized next the next table (Table IV).

Looking at the p-values in this model, only one variable is significant at the 5% level of significance: Total Duration: The log odds ratio for a one hour increase in the total duration 0.053 (95% CI: 0.0028,

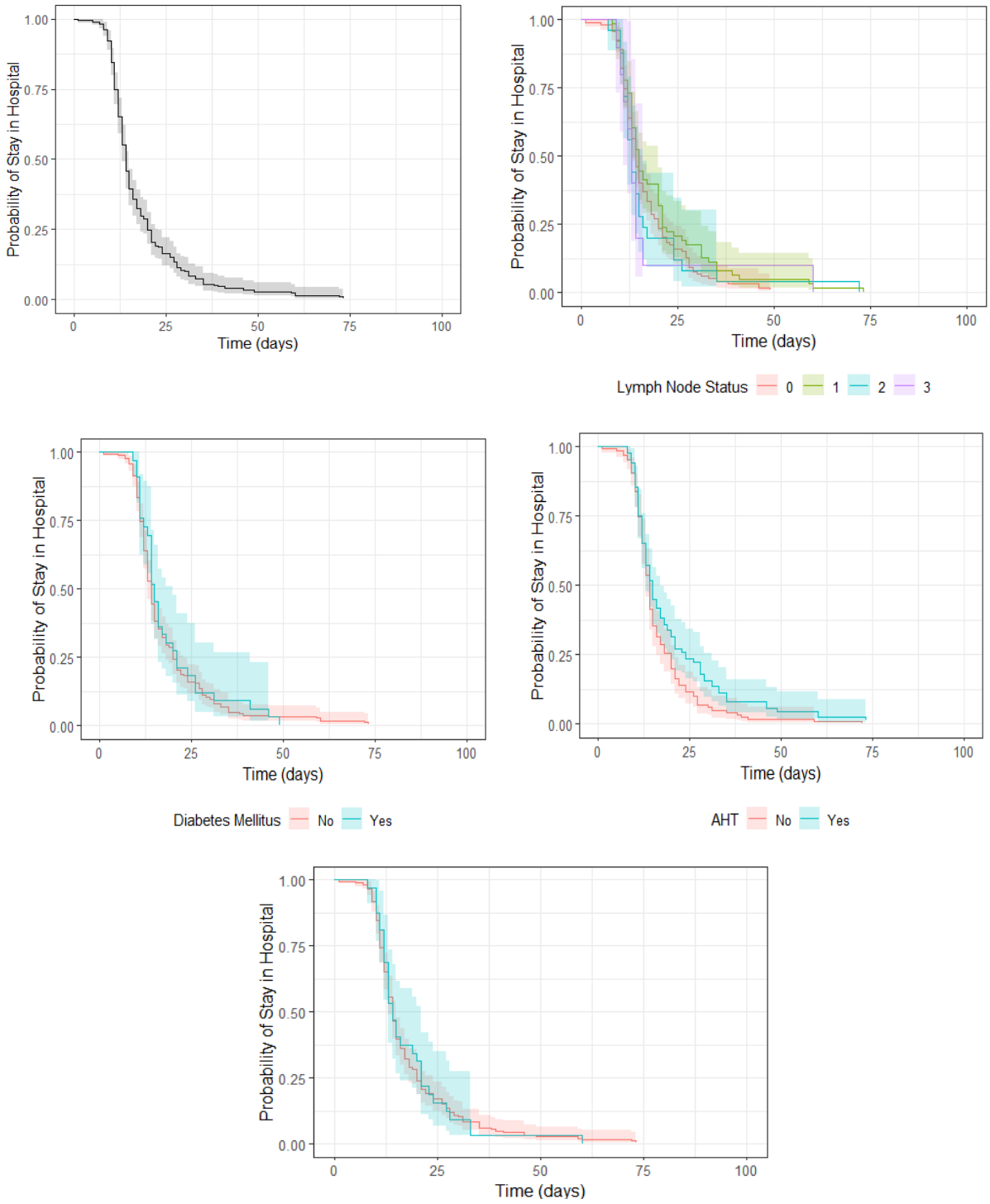

Fig. 5 — KM estimate of length of stay. Overall (5A), and stratified for Lymph Node status (5B), DM (5C), AHT (5D), and choice of fluid (5E). Shown with 95% CI.

0.1037). The p-value is 0.04.

The p-value for the treatment effect of the type of fluid is 0.991. There is thus no significant effect of the type of fluid on the probability of pneumonia, controlling for the set of measured potential confounding variables.

Discussion

This retrospective observational study showed that the administration of colloids (HES or gelatin) and crystalloids vs. only crystalloids, was not associated with an increased incidence of AKI according to KDIGO criteria. Only 2 patients suffered postoperative AKI (both KDIGO Stage 1), one in each fluid group. No meaningful statistical analysis could further be conducted.

Furthermore, this study demonstrated a small, but non-significant, benefit of adding HES or gelatins during the operation on mortality at 30-day, 90-day, and 1-year survival, controlled for the set of measured potential confounding variables. This

Table III. — COX PH model Length of stay.

Characteristic	HR	95% CI	p-value
DM			
No	—	—	
Yes	1.01	0.68, 1.49	>0.9
AHT			
No	—	—	
Yes	0.72	0.54, 0.96	0.027
Creat preop	0.78	0.46, 1.33	0.4
Hb preop	1.03	0.96, 1.11	0.4
Total duration	1.00	1.00, 1.00	0.2
Lymph Nodes status	0.96	0.81, 1.15	0.7
Total Crystalloids	1.00	1.00, 1.00	>0.9
HES or gelatines	1.07	0.73, 1.58	0.718

Table IV. — Logistic regression model postoperative pneumonia.

Characteristic	Beta	95% CI	p-value
DM			
No	—	—	
Yes	0.108	-0.071, 0.288	0.2
AHT			
No	—	—	
Yes	-0.007	-0.138, 0.124	>0.9
Creat preop	-0.125	-0.321, 0.071	0.2
Hb preop	-0.001	-0.039, 0.037	>0.9
Total duration/60	0.053	0.003, 0.104	0.040
Lymph Nodes Status	-0.023	-0.101, 0.054	0.6
Total Crystalloids	0.000	0.000, 0.000	0.7
HES or gelatines	-0.001	-0.182, 0.180	0.991

effect was more outspoken on the 1-year survival than the 30-day or 90-day survival. This is due to the fact that the overall mortality at 30 days or 90 days was very low, so any difference in effect would also be very low and insignificant. No evidence for an effect of the type of fluid on the length of stay could be detected. Lastly, no significant effect of the type of fluid on the probability of pneumonia was found, controlling for the set of measured potential confounding variables.

Of these measured potential confounding variables, lymph node status was found to be the strongest prognostic factor for survival, with a higher lymph node status having a negative impact on survival, with an estimated hazard ratio for a one-stage increase of 2.022 (95% CI: 1.595, 2.565; p-value < 0.001). Similarly, a 1-unit increase of preoperative hemoglobin (g/dl) was found to have a positive impact on survival, with an estimated hazard ratio of 0.841 (95% CI: 0.724, 0.976; p-value: 0.023). When looking at LOS, only the presence of arterial hypertension (AHT) increased the probability of a longer LOS, with an hazard ratio of 0.719 (95% CI: 0.537, 0.964; p-value: 0.027). Lastly, when looking at postoperative pneumonia,

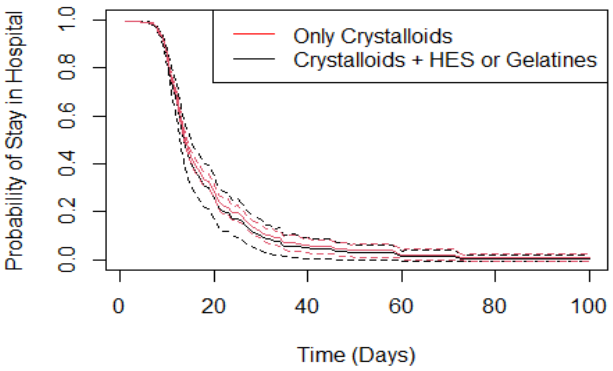

Fig. 6 — Counterfactual length of stay function with 95% CI.

only longer total operative duration increased the probability of pneumonia, with a one hour increase in the total duration showing a log odds ratio 0.053 (95% CI: 0.0028, 0.1037; p-value: 0.04).

These results are comparable with previous large RCTs, systematic reviews, and meta-analyses comparing crystalloids vs. colloids perioperatively, where no significant difference could be detected for mortality and postoperative complications such as AKI[29,35,36,40-42,45,48].

Concordantly, in this study, no positive effect from using colloids perioperatively could be detected, apart from a slight non-significant benefit on 1-year survival. This is in contrast with some recent RCTs and meta-analyses that suggest perioperative use of colloids could have a beneficial effect when used appropriately[23,25,49].

As such these findings of no significant difference could be interpreted in different ways. Firstly, given the absence of demonstrable benefit, some studies do not support the use of colloids intraoperatively, given the older trials with increased risk of death and AKI in critically ill patients[3,18,28]. On the other hand, some suggest that since no difference in outcomes seems to be found in surgical patients, colloids might have a place in selected patients for perioperative fluid resuscitation management[23,25,49]. Lastly, since most studies done on surgical patients are rather small and low quality, and subsequently reviews and meta-analyses also lack power, no demonstrable harm or benefit can for now be proven in this setting. Nonetheless, while the use of intraoperative colloids cannot be supported, studies do recommend the use of balanced crystalloids in comparison with normal saline, given the higher rates of hyperchloremic acidosis with saline[29].

Combining the evidence of potential benefit of perioperative goal-directed fluid therapy, and the ROS-D (Rescue, Optimization, Stabilization, and De-escalation) or ROSE (Resuscitation, Opitmization, Stabilization, and Evacutation) conceptual model for intravenous fluid therapy, as explained by Hoste et al.[27] and Malbrain et

al.[53] respectively; where the perioperative period consists mainly of the Rescue/Resuscitation and Optimization phase. There could be a possible place for using colloids additionally to crystalloids in order to achieve better haemodynamic stability and lower intraoperative fluid balance, when tailored to specific indications, and when avoided in patients with risk factors (such as pre-existing kidney injury and sepsis), to improve patient-centred outcomes[6,7,23,25,29,49]. However, future high quality, randomised controlled, double blind, and preferably multicentre trials based on real life perioperative settings are needed to definitively advice on fluid choice.

There are multiple obvious limitations to this present study. First and foremost, the retrospective observational nature of this study may be subject to bias from unmeasured confounding variables. Any causal interpretation acquired in this study should therefore be carefully considered. Although we attempted to control for a set of variables, we certainly could not eliminate the potential for residual confounding. Second, there was a considerable amount of missing data, for which an available case method was used, and variables with too many missing values were not used for analysis. This choice was made to retain power, however, also means that potential confounding variables were ignored. Lastly, and most importantly, only 32 patients received colloids and crystalloids (with 7 and 25 patients receiving gelatins and HES respectively), against 184 patients receiving only crystalloids. This substantially reduces the power of this study. Additionally, only 2 patients suffered postoperative AKI, therefore making it impossible to interpret this specific outcome.

Some strengths of this study may include the real-life representation of fluid management and data of MIE at the Ghent University Hospital during a 6-year period instead of a clinical setting. Additionally, the long follow-up period allowed us to examine long-term data such as 1-year survival, rather than only focusing on short term outcomes.

Conclusions

In this retrospective observational study, the administration of intraoperative colloids (HES or gelatines) alongside with crystalloids during MIE, was not associated with an increase in the incidence of AKI, mortality, length of stay, or postoperative pneumonia, when compared with only crystalloids.

Acknowledgment: We thank the relevant doctors in the services of Abdominal Surgery, Intensive Care Unit, and Anaesthesiology at the Ghent University Hospital for their help in collecting the data.

Funding and disclosure of interest: The authors declare no conflicts of interest. No financial support was provided to perform this study.

Data sharing policy: All authors agree on sharing data reported in this study. Please contact the corresponding author.

References

1. Ahn HJ, Kim JA, Lee AR, Yang M, Jung HJ, Heo B. The risk of acute kidney injury from fluid restriction and hydroxyethyl starch in thoracic surgery. Anesth Analg. 2016;122(1):186–93.
2. Low DE, Allum W, De Manzoni G, Ferri L, Immanuel A, Kuppusamy M, et al. Guidelines for perioperative care in esophagectomy: Enhanced recovery after surgery (ERAS®) society recommendations. World J Surg. 2019;43(2):299–330.
3. Gillies MA, Habicher M, Jhanji S, Sander M, Mythen M, Hamilton M, et al. Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis. Br J Anaesth. 2014;112(1):25–34.
4. Rucklidge M, Sanders D, Martin A. Anaesthesia for minimally invasive oesophagectomy. Contin Educ Anaesth Crit Care Pain. 2010;10(2):43–7
5. Gemmill EH, Humes DJ, Catton JA. Systematic review of enhanced recovery after gastro-oesophageal cancer surgery. Ann R Coll Surg Engl. 2015;97(3):173–9.
6. Mukai A, Suehiro K, Watanabe R, Juri T, Hayashi Y, Tanaka K, et al. Impact of intraoperative goal-directed fluid therapy on major morbidity and mortality after transthoracic oesophagectomy: a multicentre, randomised controlled trial. Br J Anaesth. 2020;125(6):953–61.
7. Makaryus R, Miller TE, Gan TJ. Current concepts of fluid management in enhanced recovery pathways. Br J Anaesth. 2018;120(2):376–83.
8. Drakeford PA, Tham SQ, Kwek JL, Lim V, Lim CJ, How KY, et al. Acute kidney injury within an enhanced recovery after surgery (ERAS) program for colorectal surgery. World J Surg. 2022;46(1):19–33.
9. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group: Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (part 1). Crit Care 2013;17:204.
10. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247–56.
11. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364(26):2483–95.
12. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124–34.
13. Myles PS, Bellomo R, Corcoran T, Forbes A, Peyton P, Story D, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med. 2018;378(24):2263–74.
14. 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):726–33.
15. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declère AD, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: The CRISTAL randomized trial. JAMA. 2013;310(17):1809–17.

16. Heming N, Elatrous S, Jaber S, Dumenil AS, Cousson J, Forceville X, et al. Haemodynamic response to crystalloids or colloids in shock: an exploratory subgroup analysis of a randomised controlled trial. BMJ Open. 2017;7(10):e016736.
17. Heming N, Lamothe L, Jaber S, Trouillet JL, Martin C, Chevret S, et al. Morbidity and mortality of crystalloids compared to colloids in Critically Ill surgical patients: A subgroup analysis of a randomized trial: A subgroup analysis of a randomized trial. Anesthesiology. 2018;129(6):1149–58.
18. Futier E, Garot M, Godet T, Biais M, Verzilli D, Ouattara A, et al. Effect of hydroxyethyl starch vs saline for volume replacement therapy on death or postoperative complications among high-risk patients undergoing major abdominal surgery: The FLASH randomized clinical trial: The FLASH randomized clinical trial. JAMA. 2020;323(3):225–36.
19. James MFM, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth. 2011;107(5):693–702.
20. Nisula S, The FINNAKI Study Group, Kaukonen K-M, Vaara ST, Korhonen A-M, Poukkanen M, et al. Erratum to: Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med. 2013;39(4):798–798.
21. Inkinen N, Pettilä V, Lakkisto P, Kuitunen A, Jukarainen S, Bendel S, et al. Association of endothelial and glycocalyx injury biomarkers with fluid administration, development of acute kidney injury, and 90-day mortality: data from the FINNAKI observational study. Ann Intensive Care. 2019;9(1):103.
22. Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018;8:CD000567.
23. Joosten A, Delaporte A, Ickx B, Touihri K, Stany I, Barvais L, et al. Crystalloid versus colloid for intraoperative goal-directed fluid therapy using a closed-loop system: A randomized, double-blinded, controlled trial in major abdominal surgery. Anesthesiology. 2018;128(1):55–66.
24. Joosten A, Delaporte A, Mortier J, Ickx B, Van Obbergh L, Vincent J-L, et al. Long-term impact of crystalloid versus colloid solutions on renal function and disability-free survival after major abdominal surgery. Anesthesiology. 2019;130(2):227–36.
25. Chappell D, van der Linden P, Ripollés-Melchor J, James MFM. Safety and efficacy of tetrastarches in surgery and trauma: a systematic review and meta-analysis of randomised controlled trials. Br J Anaesth. 2021;127(4):556–68.
26. Raghunathan K, Murray PT, Beattie WS, Lobo DN, Myburgh J, Sladen R, et al. Choice of fluid in acute illness: what should be given? An international consensus. Br J Anaesth. 2014;113(5):772–83.
27. Hoste EA, Maitland K, Brudney CS, Mehta R, Vincent J-L, Yates D, et al. Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth. 2014;113(5):740–7.
28. Teixeira JP, Van Sant LM, Nielsen ND. Pharmacology and clinical use of plasma expanders. Anaesth Intensive Care Med. 2020;21(8):427–33.
29. Boer C, Bossers SM, Koning NJ. Choice of fluid type: physiological concepts and perioperative indications. Br J Anaesth. 2018;120(2):384–96.
30. Suzuki T, Koyama K. Open randomized trial of the effects of 6% hydroxyethyl starch 130/0.4/9 and 5% albumin on safety profile, volume efficacy, and glycocalyx degradation in hepatic and pancreatic surgery. J Anesth. 2020;34(6):912–23.
31. Martin GS, Bassett P. Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: A systematic review and meta-analysis. J Crit Care. 2019;50:144–54.
32. Moerman A, Van Eeckhout C, Vanderstraeten K, De Somer F, Van Belleghem Y, De Hert S. The effect of hydroxyethyl starch 6% 130/0.4 compared with gelatin on microvascular reactivity. Anaesthesia. 2016;71(7):798–805.
33. Phillips DP, Kaynar AM, Kellum JA, Gomez H. Crystalloids vs. colloids: KO at the twelfth round? Crit Care. 2013;17(3):319.
34. Zacharias M, Mugawar M, Herbison GP, Walker RJ, Hovhannisyan K, Sivalingam P, et al. Interventions for protecting renal function in the perioperative period. Cochrane Database Syst Rev. 2013;(9):CD003590.
35. Pensier J, Deffontis L, Rollé A, Aarab Y, Capdevila M, Monet C, et al. Hydroxyethyl starch for fluid management in patients undergoing major abdominal surgery: A systematic review with meta-analysis and trial sequential analysis. Anesth Analg. 2022;134(4):686–95.
36. Raiman M, Mitchell CG, Biccard BM, Rodseth RN. Comparison of hydroxyethyl starch colloids with crystalloids for surgical patients: A systematic review and meta-analysis. Eur J Anaesthesiol. 2016;33(1):42–8.
37. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ. 2013;346(feb15 1):f839.
38. Tu M-Y, Hong S, Lu J, Liu Y-H, Deng M. Effect of strict intraoperative blood pressure management strategy on postoperative acute kidney injury in non-cardiac surgery: A meta-analysis of randomised controlled trials. Int J Clin Pract. 2021;75(11):e14570.
39. Miller TE, Mythen M, Shaw AD, Hwang S, Shenoy AV, Bershad M, et al. Association between perioperative fluid management and patient outcomes: a multicentre retrospective study. Br J Anaesth. 2021;126(3):720–9.
40. Nagore D, Candela A, Bürge M, Monedero P, Tamayo E, Alvarez J, et al. Hydroxyethyl starch and acute kidney injury in high-risk patients undergoing cardiac surgery: A prospective multicenter study. J Clin Anesth. 2021;73(110367):110367.
41. Vives M, Callejas R, Duque P, Echarri G, Wijeysundera DN, Hernandez A, et al. Modern hydroxyethyl starch and acute kidney injury after cardiac surgery: a prospective multicentre cohort. Br J Anaesth. 2016;117(4):458–63.
42. Smart L, Boyd C, Litton E, Pavey W, Vlaskovsky P, Ali U, et al. A randomised controlled trial of succinylated gelatin (4%) fluid on urinary acute kidney injury biomarkers in cardiac surgical patients. Intensive Care Med Exp. 2021;9(1):48.
43. Koponen T, Musialowicz T, Lahtinen P. Gelatin and the risk of acute kidney injury after cardiac surgery. Acta Anaesthesiol Scand. 2022;66(2):215–22.
44. Moeller C, Fleischmann C, Thomas-Rueddel D, Vlasakov V, Rochwerg B, Theurer P, et al. How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. J Crit Care. 2016;35:75–83.
45. Reiterer C, Kabon B, Zotti O, Obradovic M, Kurz A, Fleischmann E. Effect of goal-directed crystalloid- versus colloid-based fluid strategy on tissue oxygen tension: a randomised controlled trial. Br J Anaesth. 2019;123(6):768–76.
46. Skytte Larsson J, Bragadottir G, Krumbholz V, Redfors B, Sellgren J, Ricksten S-E. Effects of acute plasma volume expansion on renal perfusion, filtration, and oxygenation after cardiac surgery: a randomized study on crystalloid vs colloid. Br J Anaesth. 2015;115(5):736–42.
47. Goren O, Matot I. Perioperative acute kidney injury. Br J Anaesth. 2015;115 Suppl 2:ii3-14.
48. 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):281–9.
49. Feldheiser A, Pavlova V, Bonomo T, Jones A, Fotopoulou C, Sehouli J, et al. Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. Br J Anaesth. 2013;110(2):231–40.

50. Ertmer C, Zwißler B, Van Aken H, Christ M, Spöhr F, Schneider A, et al. Fluid therapy and outcome: a prospective observational study in 65 German intensive care units between 2010 and 2011. Ann Intensive Care. 2018;8(1).
51. Messina A, Robba C, Calabrò L, Zambelli D, Iannuzzi F, Molinari E, et al. Perioperative liberal versus restrictive fluid strategies and postoperative outcomes: a systematic review and metanalysis on randomised-controlled trials in major abdominal elective surgery. Crit Care. 2021;25(1):205
52. Weinberg L, Li M, Churilov L, Armellini A, Gibney M, Hewitt T, et al. Associations of fluid amount, type, and balance and acute kidney injury in patients undergoing major surgery. Anaesth Intensive Care. 2018;46(1):79–87.
53. Malbrain MLNG, Langer T, Annane D, Gattinoni L, Elbers P, Hahn RG, et al. Intravenous fluid therapy in the perioperative and critical care setting: Executive summary of the International Fluid Academy (IFA). Ann Intensive Care. 2020;10(1):64.
54. Moore EM, Bellomo R, Nichol AD. The meaning of acute kidney injury and its relevance to intensive care and anaesthesia. Anaesth Intensive Care. 2012;40(6):929–48.
55. Ostermann M, Straaten HMO, Forni LG. Fluid overload and acute kidney injury: cause or consequence? Crit Care. 2015;19(1):443

doi.org/10.56126/75.S1.24