Systematic Review & Meta-Analysis

Impact of fluid and haemodynamic management in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy on postoperative outcomes – A systematic review

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ABSTRACT

Background and Aims: Cytoreduction surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is an extensive surgery associated with significant fluid shift and blood loss. The haemodynamic management and fluid therapy protocol may impact postoperative outcomes. This systematic review was conducted to find the effect of haemodynamic monitoring and perioperative fluid therapy in CRS-HIPEC on postoperative outcomes. **Methods:** We searched PubMed, Scopus and Google Scholar. All studies published between 2010 and 2022 involving CRS-HIPEC surgeries that compared the effect of fluid therapy and haemodynamic monitoring on postoperative outcomes were included. Keywords for database searches included a combination of Medical Subject Headings terms and plain text related to the CRS-HIPEC procedure. The risk of bias and the certainty assessment were done by Risk of Bias-2 and the methodological index for non-randomised studies. **Results:** The review included 16 published studies out of 388 articles. The studies were heterogeneous concerning the design type and parameter measures. The studies with goal-directed fluid therapy protocol had a duration of intensive care unit (ICU) stay that varied from 1 to 20 days, while mortality varied from 0% to 9.5%. The choice of fluid, crystalloid versus colloid, remains inconclusive. The studies that compared crystalloids and colloids for perioperative fluid management did not show a difference in clinical outcomes. **Conclusion:** The interpretation of the available literature is challenging because the definitions of various fluid regimens and haemodynamic goals are not uniform among studies. An individualised approach to perioperative fluid therapy and a justified dynamic index cut-off for haemodynamic monitoring seem reasonable for CRS-HIPEC procedures.

Key words: Cytoreduction surgical procedures, fluid therapy, haemodynamic monitoring, hyperthermic intraperitoneal chemotherapy, postoperative outcomes, surgery

INTRODUCTION

Cytoreduction surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) involves extensive cytoreduction to decrease the tumour load. It requires a longer duration, and chemotherapy solution heated to 40–43°C is infused into the peritoneal cavity for 30–120 min. CRS-HIPEC is associated with haemodynamic disturbances, significant fluid shifts and perioperative blood loss. High core temperatures

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and inflammatory mediators released by damaged malignant cells cause a hyperdynamic circulatory state characterised by a drop in systemic vascular resistance, rise in heart rate and increased cardiac output (CO).[1-3] The incidence of major perioperative complications with the CRS-HIPEC procedure ranges from 12% to 60%, and mortality is up to 5.8%.[4-7] Fluid management is one of the most frequently debated issues in perioperative care, especially for major abdominal surgeries.[8,9]

The optimum fluid therapy for cardiovascular variation during the HIPEC procedure remains unknown. Different regimens (liberal fluid therapy, goal-directed fluid therapy [GDFT], restrictive fluid therapy) for perioperative fluid management have been debated. Both static and dynamic haemodynamic monitoring during HIPEC have been used, but their impact on fluid management and patient outcome is not defined. Recently, the introduction of hypotension prediction index and other parameters like dP/dt_{max} helped prevent hypotension and guide fluid or vasopressor requirement.[10]

Understanding the 'appropriate fluid therapy and haemodynamic monitoring' protocol for CRS-HIPEC remains inconclusive. This systematic review aims to know how much and which fluids are used, what haemodynamic monitoring is used and the common postoperative complications encountered in patients undergoing CRS-HIPEC.

METHODS

This review protocol was registered on International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022363739). The primary objective of this systematic review was to find fluid therapy and haemodynamic monitoring used for CRS-HIPEC, and the secondary objectives were postoperative outcomes, which included length of stay in the intensive care unit (ICU) or post-anaesthesia care unit (PACU), length of hospital stay, major complications and mortality. The outcomes of fluid therapy and haemodynamic monitoring during CRS-HIPEC were recorded in terms of (1) intraoperative blood loss, (2) haemodynamic stability, (3) perioperative complications: surgical site infections, anastomotic leaks, bowel perforation, renal dysfunction, cardiovascular and respiratory complications, bleeding and others; the grading and severity of complications were classified by the 'Clavien-Dindo classification' or the 'National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE)', (4) postoperative length of hospital stays and (5) postoperative mortality within a specified period.

Selection criteria

All randomised controlled trials (RCTs), non-randomised controlled trials, clinical trials, cohort studies and observational studies published between 2010 and 2022 addressing patients posted for CRS-HIPEC surgeries in gastrointestinal or gynaecological cancers which described and compared the effect of perioperative fluid therapy and haemodynamic monitoring on postoperative outcome involving any age, gender and race were included in this systematic review. Animal model studies, CRS without HIPEC procedure, studies with incomplete text and conference proceedings were excluded. We selected papers published in the English language only.

Search strategies and data collection

The literature search was conducted on PubMed, Scopus and Google Scholar. Keywords for database searches included a combination of Medical Subject Headings terms and plain text related to the CRS-HIPEC procedure. In terms of data collection, the protocol of this systematic review specified the criteria of outcome measures, time points and analyses. The protocol also specified any exclusion criteria or other factors that impact the outcome selection. The search strategies included the terms 'cytoreductive surgery', 'hyperthermic intraperitoneal chemotherapy', 'HIPEC', 'heated chemotherapy', 'haemodynamics', 'haemodynamic monitoring', 'perioperative fluid', 'fluid therapy' and their various combinations using Boolean terms. The last search was done on 15 Oct 2022.

Independent reviewers (IM and JS) screened the articles for titles and abstracts. Studies were 'included' if the selection criteria were met. In case of doubt, if any, they were resolved by the other author (SLS). Full-text articles were retrieved. The final inclusion of any study was based on full-text reading. Two review authors (IM and JS) independently extracted data from the included studies, and the data was rechecked by a third review author (SLS). A spreadsheet-based data extraction form was used to collect study information, including the year of publication, place of study, type of study, inclusion/exclusion criteria, intraoperative

chemotherapy, fluid therapy, haemodynamic target and postoperative outcomes. The interventions were considered on the following dimensions: type of fluid therapy, haemodynamic monitoring and haemodynamic monitoring target. As we planned only qualitative analysis of available data, alternative data synthesis methods were not considered.

The risk of bias and the certainty assessment was done by Risk of Bias-2 (RoB-2) and the methodological index for non-randomised studies (MINORS) [Tables 1a and 1b].[11,12] These tools were accompanied by Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) and statistical methods, wherever needed, to provide a more comprehensive assessment of the certainty of evidence.[11,12]

RESULTS

Three hundred eighty-eight articles were identified. After title and abstract review and removal of duplicates, 21 full-text articles were assessed for eligibility [Figure 1]. Data from 16 articles, which included 960 patients, were considered for this systematic review.[1,2,6,13-25]

Table 1a: Risk of bias assessments for randomised control trials using RoB-2

	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome Assessment	Incomplete outcome Data	Selective outcome Reporting	Other sources of bias	Overall score
Reis *et al*., 2020[13]	1	1	2	2	0	0	1	7
Colantonio *et al*., 2015[6]	0	1	1	0	0	0	1	3
De Witte *et al*., 2019[14]	2	1	2	2	0	0	1	8

RoB-2=the Cochrane risk-of-bias tool for randomised trials version 2: 0- low risk of bias; 1- uncertain risk of bias; 2- high risk of bias

Table 1b: Risk of bias for non-randomised trials using MINORS criteria

	Clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study
Schluermann *et al*., 2016[15]	2	2	2	2	0	2
Redondo *et al*., 2017[16]	2	2	2	2	0	2
Kajdi *et al*., 2014[17]	2	2	2	2	0	2
Shiralkar *et al*., 2017[18]	2	2	2	2	0	2
Kim *et al*., 2021[19]	2	2	2	2	0	2
Eng *et al*., 2017[20]	2	2	1	2	0	2
Hendrix *et al*., 2018[21]	2	2	2	2	0	2
Almerey *et al*., 2018[22]	2	2	2	2	0	2
Esteve-Pérez *et al*., 2018[23]	2	2	2	2	0	2
Owusu-Agyemang *et al*., 2012[24]	2	2	2	2	0	2
Thanigaimani *et al*., 2013[25]	2	2	2	2	0	1
Balakrishnan *et al*., 2020[1]	2	2	2	2	0	2
Malfroy *et al*., 2016[2]	2	2	1	2	0	2

	Loss to follow-up <5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total
Schluermann *et al*., 2016[15]	2	0	NA	NA	NA	NA	12/16
Redondo *et al*., 2017[16]	2	0	NA	NA	NA	NA	12/16
Kajdi *et al*., 2014[17]	2	1	NA	NA	NA	NA	13/16
Shiralkar *et al*., 2017[18]	2	1	NA	NA	NA	NA	13/16
Kim *et al*., 2021[19]	2	1	NA	NA	NA	NA	13/16
Eng *et al*., 2017[20]	2	0	NA	NA	NA	NA	11/16
Hendrix *et al*., 2018[21]	2	1	NA	NA	NA	NA	13/16
Almerey *et al*., 2018[22]	2	1	NA	NA	NA	NA	13/16
Esteve-Pérez *et al*., 2018[23]	2	1	NA	NA	NA	NA	13/16
Owusu-Agyemang *et al*., 2012[24]	1	2	NA	NA	NA	NA	13/16
Thanigaimani *et al*., 2013[25]	2	1	NA	NA	NA	NA	12/16
Balakrishnan *et al*., 2020[1]	2	1	NA	NA	NA	NA	13/16
Malfroy *et al*., 2016[2]	2	1	NA	NA	NA	NA	12/16

MINORS=Methodological index for non-randomised studies: 0- not reported; 1- when reported but inadequate and 2- when reported and adequate

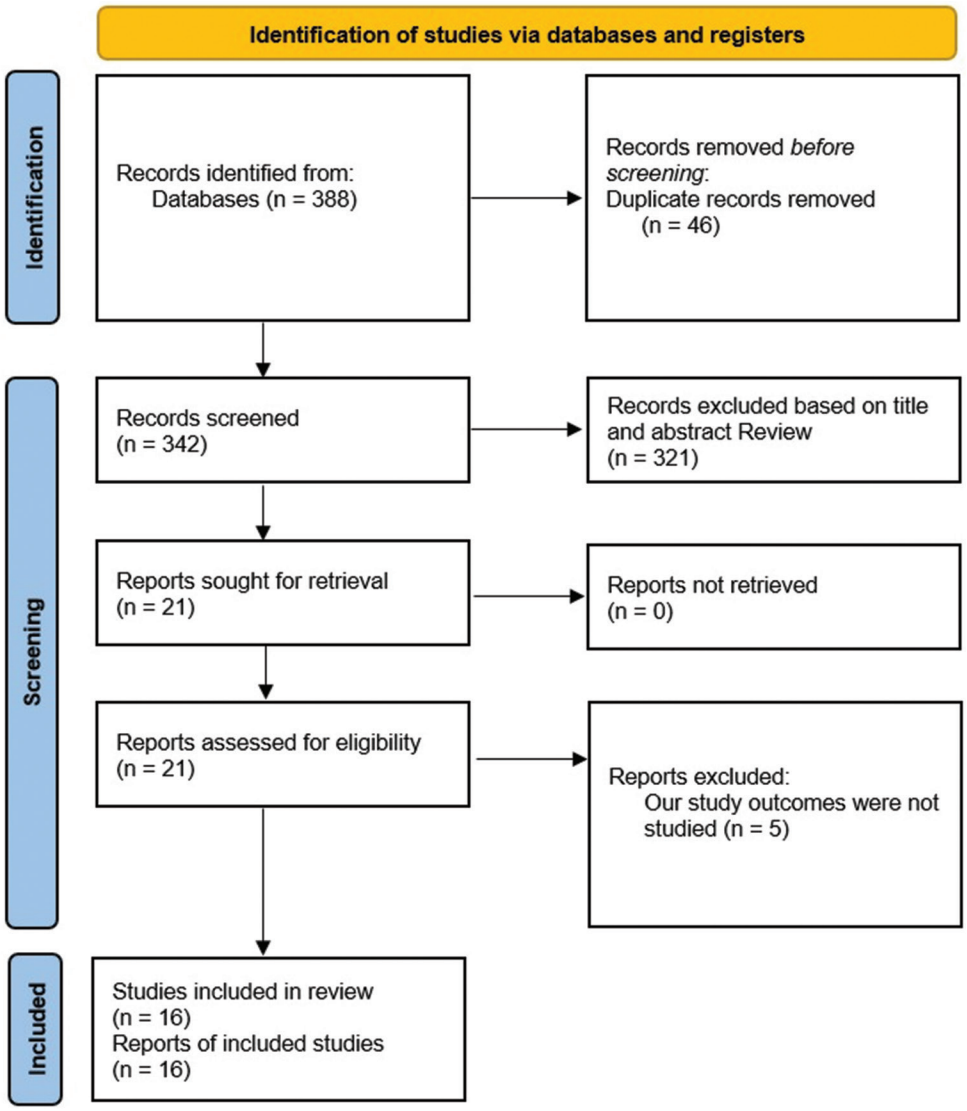

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

The risk of bias in individual studies was assessed [Tables 1a and 1b]. None of the non-randomised studies included in this review have reported blinding during the evaluation of study endpoints. Also, none of these studies used a comparator.[1,2,13,15-21,22-25] All RCTs had an uncertain or high risk of bias for allocation concealment and blinding processes.[6,13,14]

The studies included in this review were heterogeneous and varied in design [Table 2]. As the studies were heterogeneous, statistical pooling and meta-analysis were not possible. Narrative synthesis by making a qualitative summary of available data was performed.

Of the 16 studies, only three were RCTs.[6,13,14] One study included the paediatric population,[24] while the rest of the study population was adults. The mean age of patients in the included adult studies was 54.7 years (range 19 to 84 years). The mean age in the paediatric study was 5.8 years (range 3–9 years).[24]

Only seven of 16 included studies mentioned the disease load (peritoneal cancer index). Most included patients who belonged to the American Society of Anesthesiologists (ASA) physical status I–III, and 14 out of 16 studies mentioned invasive haemodynamic monitoring (invasive blood pressure, central venous pressure [CVP] and CO monitoring).[1,2,6,13-19,21,23-25] Several chemotherapy drugs were commonly utilised in the studies mentioned. Mitomycin C[1,2,14,15,17,18,20-23] and cisplatin[1,2,12,13,17,20-24] emerged as frequently employed drugs in 10 studies. The use of oxaliplatin,[1,2,23] paclitaxel[16,23], and carboplatin[21] was also mentioned in different studies. The mean duration of surgery

Table 2: Demographic characteristics

Authors	Country	Study design	Study period	Number of patients	Type of malignancy
Schluermann *et al*., 2016[15]	Germany	Prospective observational study	Not available	10	Mixed
Redondo *et al*., 2017[16]	Spain	Clinical pilot study	Not available	18	Ovarian
Kajdi *et al*., 2014[17]	Switzerland	Retrospective analysis	2009–2011	57	Mixed
Shiralkar *et al*., 2017[18]	Australia	Retrospective audit	2009–2015	70	Mixed
Reis *et al*., 2020[13]	Italy	Randomised controlled trial	2014–2017	33	Mixed
Kim *et al*., 2021[19]	South Korea	Prospective observational study	2014–2016	21	Mixed
Colantonio *et al*., 2015 [6]	Italy	Randomised controlled trial	2010–2012	80	Mixed
Eng *et al*., 2017[20]	California	Retrospective cohort	2009– 2016	133	Mixed
Hendrix *et al*., 2018[21]	Massachusetts	Retrospective cohort study	2009–2017	169	Mixed
De Witte *et al*., 2019[14]	The Netherlands	Randomised controlled trial	2011–2014	24	Not available
Almerey *et al*., 2018[22]	Florida	Retrospective cohort study	2015–2017	35	Mixed
Esteve-Pérez *et al*., 2018[23]	Spain	Prospective observational study	2014–2017	92	Mixed
Owusu-Agyemang *et al*., 2012[24]	Texas	Phase 1 trial	2005–2009	6	Sarcomatosis
Thanigaimani *et al*., 2013[25]	UK	Prospective	2009–2010	25	Mixed
Balakrishnan *et al*., 2020[1]	India	Retrospective analysis	2014–2019	65	Mixed
Malfroy *et al*., 2016[2]	France	Retrospective cohort study	2010–2011	122	Not available

Authors	Age group (years)	ASA 1/2/3	PCI
Schluermann *et al*., 2016[15]	54 (40–73); median (range)	ASA 2–3 (8/2)	Not available
Redondo *et al*., 2017[16]	57 (42–84); median (range)	Not available	Not available
Kajdi *et al*., 2014[17]	52 (20–72); median (range)	ASA 1/2/3=5/49/3	Not available
Shiralkar *et al*., 2017[18]	52.50 (25–72); median (range)	ASA 1/2/3/4=6/23/38/3	Not available
Reis *et al*., 2020[13]	51.5 (12.6); mean (SD)	ASA 1/2/3: 20%/68%/12%	Low IAP group: 14.60 (8.30), mean (SD) High IAP group: 10.83 (7.29); mean (SD)
Kim *et al*., 2021[19]	59.0 (11.7); mean (SD)	ASA1/2/3: 9/7/5	Not available
Colantonio *et al*., 2015 [6]	GDT: 54.5 (9.8); mean (SD) Control: 57.6 (8.8); mean (SD)	ASA 3 — number (%) GDT: 4 (10.5) Control: 2 (4.8)	Not available
Eng *et al*., 2017[20]	54 (47–64); mean (IQR)	ASA 3, *n*=81	13 (7–18); mean (IQR)
Hendrix *et al*., 2018[21]	55 (16); mean (SD)	ASA 2.6 (0.8), mean (SD)	17.6 (10.4); mean (SD)
De Witte *et al*., 2019[14]	FloTrac: 60.3 (9.0); mean (SD) Standard care: 60.1 (12.1); mean (SD)	ASA >2 Flotrac/Vigileo: 1/12 Standard care: 0/12	Not available
Almerey *et al*., 2018[22]	56 (21–74); median (range)	ASA >3: 16 (46)	15 (9.5–22.5); median (IQR)
Esteve-Pérez *et al*., 2018[23]	58.5 (10.9) mean (SD)	ASA 1–2	10 (0–39) median (range)
Owusu-Agyemang *et al*., 2012[24]	5.8 (3–9); mean (range)	Not available	Not available
Thanigaimani *et al*., 2013[25]	55 (19–78); mean (range)	Not available	Not available
Balakrishnan *et al*., 2020[1]	51 (22–72); median (range)	ASA 1/2/3/4 *n* (%) 0/58 (89.2)/7 (10.7)/0	Median 15 (0–39)
Malfroy *et al*., 2016[2]	56.4 (9); Mean (SD)	ASA 1.7±0.5 (mean±SD)	12.4±7.4 (mean±SD)

ASA: American Society of Anesthesiologists, GDT: Goal Directed Therapy, IQR: interquartile range, PCI: Peritoneal Carcinomatosis Index, SD: standard deviation

based on the duration mentioned in 14 studies was 542.63 min. A total of 11 studies used GDFT.[1,2,6,13,15-19,23,25] Specific haemodynamic monitoring techniques used were Pulse Index Continuous Cardiac Output (PICCO)-based CO monitoring,[15-17] EV1000 (VolumeView™; Edwards Lifesciences, Irvine, CA, USA), Vigileo and FloTrac monitoring[6,18,19,23] and unspecified arterial pressure-based CO monitoring.[13,19] Most studies used invasive blood pressure and CVP.[13,15-19,21,24] Thanigaimani *et al*.[25] used Lithium Dilution Cardiac Output (LiDCO) monitor [Table 3a]. However, the haemodynamic targets varied across these studies and remained inconclusive. Three studies considered stroke volume variation (SVV) <10% as a target for fluid administration, while another considered SVV <15% as a target.[15-17,25]

The intraoperative fluids, urine output, blood loss and replacement, and any use of vasopressors were mentioned in all studies. A total of 10 studies mentioned crystalloids and colloids separately administered during CRS and HIPEC,[2,6,13,15,17-19,21,22,24] and five studies mentioned only the volume of fluid

Table 3a: Intraoperative details

Authors	Chemotherapy drugs	Mean duration of surgery, min	Duration of HIPEC, min	Fluid therapy used- liberal/ restrictive/goal directed	Haemodynamic monitoring
Schluermann *et al*., 2016[15]	Mitomycin Cisplatin	320 (110–570); median (range)	92 (87–98) median (range)	Goal directed	Invasive BP CVP PICCO-based cardiac output monitoring (PulsioFlex ProAQT® Monitor)
Redondo *et al*., 2017[16]	Paclitaxel	Not available	60	Goal directed	Invasive BP CVP PICCO-based cardiac output monitoring (GEDV, CI, SVV, ITBV, ELWI)
Kajdi *et al*., 2014[17]	Doxorubicin with mitomycin OR cisplatin Cisplatin with mitomycin	715 (370–1135)	60–90	Goal directed	Invasive BP CVP PICCO-based cardiac output – 48 (*n*) PAC- 3 (*n*) Both PICCO and PAC- 1 (*n*)
Shiralkar *et al*., 2017[18]	Mitomycin C	555 (195–1020)	90	Goal directed	Invasive BP CVP EV1000 monitoring system
Reis *et al*., 2020[13]	Cisplatin	527; Mean	60	Goal directed	Invasive BP CVP APCO monitoring using FloTrac (EV1000) monitoring system
Kim *et al*., 2021[19]	Not available	638.8 (207.8); Mean (SD)	90	Goal directed	Invasive BP CVP APCO monitoring using VolumeView (EV 1000) monitoring system
Colantonio *et al*., 2015[6]	Not available	Mean (SD) Control group: 9.7 (1.2) GDT group: 9.3 (1.5)	Not available	Restrictive fluid therapy- control group Goal-directed fluid therapy- GDT group	Invasive BP CVP FloTrac/Vigileo system in GDT group
Eng *et al*. 2017[20]	Mitomycin Platinum-Based	mean 8.5 hrs, IQR (6.7-10 h)	Not Available	Not Available	Not Available
Hendrix *et al*.; 2018[21]	Mitomycin C Carboplatin Doxorubicin	PFT: 9.3 h RFT: 7.8 h	Not Available	PFT- 84 patients RFT- 85 patients	Invasive BP
De Witte *et al*.; 2019[14]	Mitomycin C	Not Available	Not Available	Liberal fluid- standard care group Restrictive fluid therapy- FloTrac/ Vigileo group	FloTrac/Vigileo system in study group
Almerey *et al*.; 2018[22]	Mitomycin C Platinum-based	520 (427.5, 644.5) median (IQR)	Not Available	Restricted fluid therapy	Not Available
Esteve-Pérez *et al*.; 2018[23]	mitomycin C oxaliplatin paclitaxel cisplatin	642.5 (415–1125) Mean (range)	Not Available	Goal-directed	CVP FloTrac
Owusu-Agyemang *et al*.; 2012[24]	cisplatin	600-960	Not Available	Not Available	Invasive BP CVP
Thanigaimani *et al*.; 2013[25]	Not Available	600 (129) (SD)	60	Goal-Directed	LiDCO rapid cardiac output monitor
Balakrishnan *et al*.; 2020[1]	Cisplatin, Oxaliplatin or Mitomycin C	540 (300-1200)	Not Available	Goal-directed	FloTrac (EV1000)

Contd...

Table 3a: Contd...

Authors	Chemotherapy drugs	Mean duration of surgery, min	Duration of HIPEC, min	Fluid therapy used- liberal/ restrictive/goal directed	Haemodynamic monitoring
Malfroy *et al*.; 2016[2]	Cisplatin Mitomycin Oxaliplatin Doxorubicin 5FU Irinotecan	475±77	74 (23) mean (SD)	Goal directed	Invasive BP CVP CO using vigileo

Authors	Target used	Blood transfusion trigger	*P* or remark
Schluermann *et al*., 2016[15]	SVV <15% MAP within 20% of baseline	Hb 7 gm%	CVP increased slightly during HIPEC and returned to baseline after drainage of the abdominal cavity (*P*<0.001) SVRI decreased during HIPEC and further till the end of the procedure (*P*<0.05) CI increased throughout *P*<0.001
Redondo *et al*., 2017[16]	GEDV <800 ml/m^2 SVV <10% ITBI=850–1000 ml/m^2 and ELWI 6–8 ml/kg	Not available	No significant difference at different times (pre-, intra and post-HIPEC): HR *P*=0.305 MAP *P*=0.711 CI *P*=0.227 SVRI *P*=0.082
Kajdi *et al*., 2014[17]	SVV <10% Urine output during CRS 0.5 ml/kg/h	Not available	
Shiralkar *et al*., 2017[18]	Urine output >0.5 ml/kg/h	Hb 8 gm%	
Reis *et al*., 2020[13]	MAP >65 mmHg CI >2.0 l/m^2	Not available	CVP was significantly higher in the high IAP group (*P*=0.006)
Kim *et al*., 2021[19]	SVV, CI GEDI, ELWI and PVPI	Hb 8 gm%	
Colantonio *et al*., 2015[6]	Control group: inotropic agents (dopamine) If CVP ≤15 mmHg or UO ≤1 ml/kg/h or MAP ≤70% of preinduction GDT group: CI >2.5 l/min/m^2	Hb <8 gm% (9 gm % in patients with cardiac disease)	
Eng *et al*. 2017[20]	Not Available	Hb 7 gm%, 10 gm % for Pt with cardiac diseases	
Hendrix *et al*.; 2018[21]	PFT approach: 1000 mL/h crystalloid +/-additional colloid RFT: 500 mL/h +/- vasopressors No specified endpoint	Not Available	
De Witte *et al*.; 2019[14]	Not Available	Not Available	
Almerey *et al*.; 2018[22]	Not Available	Not Available	
Esteve-Pérez *et al*.; 2018[23]	MAP 60–80 mm Hg CVP >5 cm H2O $ScvO_2$ >75% <85% SVV 10%–13% CI ≥2.5 L/min/m^2 SVV 10%–13%	Not Available	CI increased during surgery (*r*=0.343, *P*=0.001). Heart rate significantly increased during HIPEC (*P*=0.000).
Owusu-Agyemang *et al*.; 2012[24]	Urine output >2 ml/kg/h CVP 7-12 cm H_20	Not Available	
Thanigaimani *et al*.; 2013[25]	MAP within 20% of the baseline SVV below 10%. Crystalloid 350 ml/hr + colloid boluses	Hb 8-10 gm%.	SVR changed throughout surgery but non-significant *P*=0.62
Balakrishnan *et al*.; 2020[1]	SVI	Hb 9 gm %	
Malfroy *et al*.; 2016[2]	Not Available	Not Available	

APCO: Arterial Pressure Based Cardiac Output; BP: Blood Pressure; CI: Cardiac Index, CO: Cardiac Output; CVP: Central Venous Pressure; CRS: Cytoreductive Surgery; ELWI: Extravascular Lung Water Index; GDT: Goal-Directed Therapy; GEDI: Global End-Diastolic Index; GEDV: Global End-Diastolic Volume; ITBV: Hb: Hemoglobin; Intrathoracic Blood Volume; IQR: Interquartile Range; LiDCO: Lithium Dilution Cardiac Output; MAP: Mean Arterial Pressure; PAC: Pulmonary Artery Catheter; PICCO: Pulse Index Continuous Cardiac Output; PFT: Permissive Fluid Therapy; PPV: Pulse Pressure Variation; PVPI: Pulmonary Vascular Permeability Index; RFT: Restrictive Fluid Therapy; ScvO2: Mixed Central Venous Oxygen Saturation. SD: Standard Deviation; SVI: Stroke Volume Index; SVV: Stroke Volume Variation

Table 3b: Intraoperative details

Authors	Blood Product Transfusion	Volume of Crystalloid Used (CRS)	Volume of Colloid Used (CRS)	Volume of Crystalloid Used (HIPEC)
Schluermann *et al*.; 2016[15]	Nil	4250 (1600-12000) ml Median (Range)	500 (0-1500) ml Median (Range)	2250 (1200-4000) ml Median (Range)
Redondo *et al*. 2017[16]	Not Available	Not Available	Not Available	Not Available
Kajdi *et al*.; 2014[17]	PRBC; *n*=16: 4 (1–10) units FFP; *n*=3, 6 (4–8) units Platelet; *n*=4, 1 (1-2) units Fibrinogen; *n*=21, 4 (2–22) g Prothrombin complex concentrate; *n*=9,1000 (400–2000) IU Factor XIII; *n*=13,1500 (1250–4000) IU Factor VIII-vWF; *n*=1,1000 IU Recombinant factor VII; *n*=1,1000 µg	5900 (2200–19100) ml (CRS + HIPEC)	2500 (500–14500) ml (CRS + HIPEC)	Not Available
Shiralkar *et al*.; 2017[18]	Median (range) PRBC: 1135 (248–8112) ml FFP: 1,634 (500–8711) ml Platelets: 372 (60–812) ml Cryoprecipitate: 320 (178–705) ml	7,318 (3000-28000) ml (CRS + HIPEC)	3370 (200-13700) ml (CRS + HIPEC)	Not Available
Reis *et al*.; 2020[13]	Low IAP group=PRBC: 0.87 (1.45) Units, FFP: 5.60 (7.53) ml/kg High IAP group=PRBC: 0.50 (0.98) units FFP: 2.44 (5.65) ml/kg	Low IAP group=12.94 (4.01) ml/kg/h, High IAP group=12.82 (5.27) ml/kg/h (CRS + HIPEC)	Low IAP group=1.74 (0.74) ml/kg/hr, High IAP group=1.36 (1.05) ml/kg/hr (CRS + HIPEC)	Not Available
Kim *et al*.; 2021[19]	Mean (SD, Range) PRBC: 207.1 (378.2, 0–1400) ml FFP: 71.4 (181.4, 0-600) ml	6983.3 (4496.4) ml; Mean (SD) (CRS + HIPEC)	976.2 (460.3) ml ; Mean (SD) (CRS + HIPEC) Albumin 109.5 (151.3, 0–500) ml Mean (SD, Range) (CRS + HIPEC)	Not Available
Colantonio *et al*.; 2015[6]	PRBC: *n*=1 in each group	CRS + HIPEC: Mean (SD) Control group: (6852±1413 GDT group: 3884±1003 ml; *P*<0.0001).	CRS + HIPEC: Mean (SD) Control group: 1417±279 ml GDT group: 1927±318 ml	Not Available
Eng *et al*. 2017[20]	PRBC: *n*=79 (59.4%)	Intraoperative fluid rate (CRS + HIPEC), Mean (IQR): 15.7 (11.3-18.7) ml/kg/h	Not Available	Not Available
Hendrix *et al*.; 2018[21]	PRBC: *n* (PFT): 18 *n* (RFT): 12 Mean (SD) L PFT: 2.6 (0.9) RFT: 0.04 (0.2)	Intraoperative (CRS + HIPEC) crystalloid: Mean (SD) L PFT: 8.0 (3.2) RFT: 4.4 (1.8)	Intraoperative (CRS + HIPEC) colloid: Mean (SD) L PFT: 0.9 (1.1) RFT: 0.3 (0.5)	Not Available
De Witte *et al*.; 2019[14]	PRBC: Study group: 150±170 ml Control Group: 250±110 mL	Total amount of fluid in first 24 h: Study group: 10,437±987 ml Control Group: 8,135±760 mL	Not Available	Not Available
Almerey *et al*.; 2018[22]	PRBC: 700 (612, 1150) ml Median (IQR)	(CRS + HIPEC) : Median (IQR) 1900 (1000, 3200) ml	(CRS + HIPEC): Median (IQR) 1500 (1000, 2000) ml	Not Available

Contd...

Table 3b: Contd...

Authors	Blood Product Transfusion	Volume of Crystalloid Used (CRS)	Volume of Colloid Used (CRS)	Volume of Crystalloid Used (HIPEC)
Esteve-Pérez *et al*.; 2018[23]	PRBC: 30% of the patients, an average of 2 units per patient	Intraoperative fluid therapy (CRS + HIPEC): median range: 9.8 ml/kg/h [5.3–24.3]	Not Available	Not Available
Owusu-Agyemang *et al*.; 2012[24]	PRBC: mean 15 ml/kg	(CRS + HIPEC): Mean 106 ml/kg or 8 ml/kg/h.	(CRS + HIPEC) mean 25 ml/kg	Not Available
Thanigaimani *et al*.; 2013[25]	PRBC: 2.54±2.6 units FFP: 2.9±2.2 units	(CRS + HIPEC) crystalloid + colloid : First 30 min 748 + next 30 min 631.8 + next 30 min 507.66 ml	Not Available	Not Available
Balakrishnan *et al*.; 2020[1]	PRBC: Median (range) 500 ml (0-4000) FFP: Median (range) 600 ml (0-2100)	Intraoperative fluid therapy (CRS + HIPEC) (crystolloid + colloid): Median range; 5.5 (2-5-19.5) L	Not Available	Not Available
Malfroy *et al*.; 2016[2]	Percentage of patients; PRBC: 30% Platelets: 2.5% FFP: 10%	CRS + HIPEC (ml/kg/h) (mean±SD) 9.0±2.5	CRS + HIPEC Hydroxyethyl starch (ml) (mean±SD) 802±410 Albumin 4% (ml) (mean±SD) 777±370	Not Available

Authors	Volume of Colloid Used (HIPEC)	Blood Loss (ml)	Urine output (ml)	Mean Arterial Lactates end of HIPEC	Intraoperative Vasopressors
Schluermann *et al*.; 2016[15]	0 (0-500) ml Median (Range)	275 (0-750) ml medians (range)	CRS-0.8 (0.3-1.8) HIPEC-0.5 (0.17-1.2) ml/kg/h	2.7 (1.1) Mean (SD)	Noradrenaline
Redondo *et al*. 2017[16]	Not Available	809 ± (714) Mean (SD)	902 ± (399) Mean (SD)	3.20±1.53 Mean (SD)	Not Available
Kajdi *et al*.; 2014[17]	Not Available	800 (0–6000) ml median (range)	1460 (330–3970) ml	Not Available	Noradrenaline
Shiralkar *et al*.; 2017[18]	Not Available	500 (0-10000) ml median (range)	Median 2.76 ml/kg/hour	Not Available	Noradrenaline (n=58, 83% patients)
Reis *et al*.; 2020[13]	Not Available	Not Available	Not Available	Low IAP group=2.1 (2.4), High IAP group=1.7 (1.0)	Noradrenaline Adrenaline
Kim *et al*.; 2021[19]	Not Available	780.0 (928.6, 50–3350) ml	1464.8 (898.0) ml; Mean (SD)	3.1 (1.8) Mean (SD)	Phenylephrine *n*=15 (71.4%) Noradrenaline *n*=2 (9.5%)
Colantonio *et al*.; 2015[6]	Not Available	mean (SD) Control group: 1089 (1230) ml GDT group: 980 (885) ml	mean (SD) Control group: 2506 (474) ml GDT group: 2385 (211) ml	mean (SD) Control group: 2.66±1.25 ml GDT group: 1.94±0.77 ml	Dopamine Control group: *n*-5 GDT group: *n*=23
Eng *et al*. 2017[20]	Not Available	mean 932 (IQR 300-1000 ml)	mean (IQR), mL 1620 (800-2200)	Not Available	Not Available
Hendrix *et al*.; 2018[21]	Not Available	L [mean (SD)] PFT: 0.44 (0.3), RFT 0.34 (0.3) 0.05	Not Available	Not Available	Not Available
De Witte *et al*.; 2019[14]	Not Available	Not Available	Not Available	Not Available	Not Available
Almerey *et al*.; 2018[22]	Not Available	Median (IQR) 400 (200-725) ml	Median: (IQR) 1.9 (1.3-3.1) mL/kg/h	Not Available	Continuous infusion of vasopressin 0.02 units/h
Esteve-Pérez *et al*.; 2018[23]	Not Available	(mean range) 500 ml [0–4000]	(mean range) 1.3 ml/Kg/h [0.8–4.1]	Not Available	Noradrenaline, *n* (%) 31 (34%)
Owusu-Agyemang *et al*.; 2012[24]	Not Available	12 ml/kg	mean 3 ml/kg/hr	Not Available	nil

Contd...

Table 3b: Contd...

Authors	Volume of Colloid Used (HIPEC)	Blood Loss (ml)	Urine output (ml)	Mean Arterial Lactates end of HIPEC	Intraoperative Vasopressors
Thanigaimani *et al*.; 2013[25]	Not Available	The average blood loss during surgery was 1820±809 ml.	first 30 min 307.4, next 30 min 319.8, next 30 min 199.41 ml	30 min: 1.96 60 min: 1.92 90 min: 1.51	phenylephrine
Balakrishnan *et al*.; 2020[1]	Not Available	1000 ml (100-6500)	Not Available	Not Available	Not Available
Malfroy *et al*.; 2016[2]	Not Available	376.6±286.6 ml	863±347 ml	Not Available	Ephedrine Noradrenaline Dobutamine

CRS: Cytoreductive Surgery; GDT: Goal-Directed Therapy; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; IAP: Intra-Abdominal Pressure; IQR: Interquartile Range; PFT: Permissive Fluid Therapy; RFT: Restrictive Fluid Therapy; SD: Standard Deviation; n: Number of patients, PRBC: Packed red blood cells, FFP: Fresh Frozen Plasma

administered during the whole surgery.[1,14,20,23,25] Redondo *et al*.[16] did not mention fluid therapy but was included in the analysis because of other outcomes of interest. The median (interquartile range [IQR]) crystalloid replacement was 5594 (4125–7318) ml, while the median (IQR) colloids transfused was 2250 (1475–3250) ml approximately.

In the study which reported the amount of fluid administered during CRS and HIPEC separately, the median (range) volume of crystalloid used was 4250 ml (1600–12,000 ml) and 2250 ml (1200–4000 ml) during the CRS and HIPEC phases, respectively.[15] The median (range) amount of colloid used during CRS was 500 ml (0–1500 ml), whereas the HIPEC phase used 0 (0–500) ml of colloid.[15] In studies which reported the total amount of fluid administered during CRS-HIPEC, the median (range) volume of crystalloid used during CRS-HIPEC was 5900 ml (2200–19,100 ml) and the median (range) volume of colloid used during CRS-HIPEC was 2500 ml (500–14,500 ml).

Except for one study, none of the included studies mentioned the fluid volume used in two different phases.[15] Thus, subgroup analysis on the type of fluid management for two different phases was not possible. None of the included studies mentioned acid–base disturbance related to fluid administration. None of the studies mentioned the type of crystalloid fluid used except one, which used plasmalyte.[23] The choice of vasopressor also varied across the studies, which included dopamine, noradrenaline, vasopressin and phenylephrine.[15-19,23] The median (IQR) urine output was 1.3 (0.9–2.76) ml/h. The mean arterial lactates was 2.343 mmol/l [Table 3b].

The median (IQR) blood loss was 780 (500–3000) ml. Seven studies out of 16 mentioned transfusion triggers; however, this value was not uniform.[1,6,15,18-20,25] The transfusion trigger varied from 7 to 10 gm%. The mean (range) blood transfusion was 244.79 (0–8112) ml. The mean number of packed blood cell units ranged from 0.5 to 10 units. One study on the paediatric population used a mean packed blood cell volume of 15 ml/kg. Out of 16 total studies, six studies have also used other blood products like platelet concentrate, fresh frozen plasma (FFP) and packed red blood cells (RBCs)[1,2,13,17-19,25] [Table 3b]. However, the included studies did not mention specific coagulation abnormality as an indication for transfusion of the blood product, except one[17], which mentioned the use of routine laboratory tests and rotational thromboelastogram to diagnose coagulation abnormalities. Only one study mentioned using fibrinogen, prothrombin complex concentrate, factor XIII, factor VIII–vWF, recombinant factor VII beside FFP, and platelets.[17]

The postoperative outcomes in terms of length of ICU or PACU stay were mentioned by six out of 16 studies and varied from a median of 1 to 4.6 days (range 0–70 days). The median/mean length of hospital stay was 7–27 days, as mentioned in 10 studies. Irrespective of fluid therapy protocol and haemodynamic monitoring, 8%–38% of patients had major complications in 12 studies,[2,6,13,14,17-23,25] while others did not mention postoperative complications.[1,15,16,24] Seven out of 12 studies defined major complications as per Clavien–Dindo classification ≥3 or National Cancer Institute-Common Terminology Criteria for Adverse Events >3. In contrast, other studies mentioned postoperative complications such as pulmonary complications, haemodynamic instability, etc., or did not specify. However, the overall mortality varied from 0%–16% [Table 4].

Table 4: Postoperative details

Authors	Length of ICU/ PACU Stay; Days	Length of Hospital Stay; Days	Major Postoperative Complications; *n* (%)	Mortality; *n* (%)
Schluermann *et al*.; 2016[15]	4 (2-7); Median (Range)	16.5 (8-47); Median (Range)	Not Available	Not Available
Redondo *et al*. 2017[16]	Not Available	Not Available	Not Available	Not Available
Kajdi *et al*.; 2014[17]	2 (1–35); Median (Range)	17 (9–259); Median (Range)	12 (21%); CD >3b	2 (4%)
Shiralkar *et al*.; 2017[18]	1 (0-8); Median (Range)	22.5 (4-335); Median (Range)	24 (34%); CD 3-5	4 (5.7%)
Reis *et al*.; 2020[13]	Not Available	Not Available	Low IAP=8.8%; (NCI-CTCAE G3-5) High IAP=10.5%; (NCI-CTCAE G3-5)	1 (3%)
Kim *et al*. ; 2021[19]	1.4 (1.3); Mean (SD)	18.5 (10.2); Mean (SD)	7 (33.3%)	2 (9.5%)
Colantonio *et al*.; 2015[6]	Not Available	Control group: 29; Median GDT group: 19; Median	Control group: 38.1% GDT group: 10.5%	Control group: 9.5%, GDT group: 0%
Eng *et al*.; 2017[20]	2 (2-3); Median (Range)	10.5 (8-15); Median (Range)	42 (31.6%), CD≥3a	30-day Mortality: 0
Hendrix *et al*.; 2018[21]	Not Available	PFT: 11.5; Mean (SD) RFT: 9.7; Mean (SD)	14.2%; CD≥3	90-day mortality PFT: 1.2% RFT: 0%
De Witte *et al*.; 2019[14]	Not Available	Not Available	FloTrac: 2 (16%) Standard care: 5 (41%)	30-day mortality: FloTrac: 0 Standard care: 2 (16%)
Almerey *et al*.; 2018[22]	Not Available	7 (6-8.5); median (IQR)	5 (14%); CD3-4	30 Day Mortality: 0 90 Day Mortality: 1 (2.8%)
Esteve-Pérez *et al*.; 2018[23]	4.6 (2–70); Mean (Range)	18.3 (7–110); Mean (Range)	26% (24/92); CD3-4	1 (1%)
Owusu-Agyemang *et al*.; 2012[24]	Not Available	Not Available	Not Available	Not Available
Thanigaimani *et al*.; 2013[25]	Not Available	Not Available	2 (8%)	Not Available
Balakrishnan *et al*.; 2020[1]	Not Available	15 (9-58); Median (Range)	Not Available	Not Available
Malfroy *et al*., 2016[2]	0.8 (0.2); mean (SD)	Not available	32 (26.2%)	7 (5.7%)

ICU: Intensive Care Unit; IQR: Interquartile Range; CD: Clavien Dindo Classification; PACU: Post-Anaesthesia Care Unit; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events; PFT: Permissive Fluid Therapy; RFT: Restrictive Fluid Therapy; SD: Standard Deviation

DISCUSSION

Evidence on the effects of type of fluid management and haemodynamic monitoring during CRS-HIPEC procedures on postoperative outcome is uncertain due to the availability of either heterogeneous data or no data.

Fluid overload during liberal fluid therapy may lead to multi-organ dysfunction and delayed recovery.[26] Earlier recommendations favoured liberal fluid therapy during the CRS-HIPEC procedures as high as 1500 ml/h.[27] However, liberal fluid therapy during the CRS-HIPEC procedure exposes the patient to the risk of fluid overload. The intraoperative fluid administration rate was an independent predictor of higher morbidity.[20] Due to recognised complications, there is a gradual shift towards a more restrictive approach to the HIPEC procedure. Many institutions included restrictive fluid therapy or GDFT, which resulted in lower morbidity and mortality[6,20,21] [Table 3b].

In GDFT, fluid is administered until prespecified haemodynamic targets of cardiac index (CI), stroke volume (SV), SVV, pulse pressure variation (PPV), serum lactate levels, superior vena cava oxygen saturation, etc., are achieved.[28,29] A vasopressor is added as per haemodynamic parameters after ensuring optimal intravascular volume status. GDFT using SVV monitoring in CRS-HIPEC has been shown to tailor the fluid requirement individually. GDFT minimises the risks of renal failure due to intravascular volume depletion and tissue oedema due to fluid overload. GDFT, as part of the enhanced recovery after surgery (ERAS) protocol, showed improved postoperative outcomes, including the early return of bowel function and decreased length of stay after CRS-HIPEC.[5]

The use of GDFT for HIPEC procedures showed a shorter hospital length of stay (19 vs. 29 days), a lower incidence of major abdominal complications (10.5% vs. 38%) and comparable mortality compared to

standard fluid therapy.[6] The studies with the GDFT protocol reported a varied median duration of ICU stay (1–20 days), while mortality varied from 0% to 9.5%.[1,2,6,13,17-19,23] The expert committee of the Society of Onco-Anaesthesia and Perioperative Care (SOAPC) and the ERAS Society gave consensus independently for the use of individualised GDFT during the CRS-HIPEC procedure.[30,31]

The restrictive fluid therapy/zero-balance approach replaces only fluid loss during surgery. The patients receive crystalloid solution at a rate of 1–3 ml/kg/h to replace sensible and insensible losses during the intraoperative period without any preloading before induction of anaesthesia and replacement for third space loss. Any blood loss is replaced by crystalloid or colloid with a volume ratio of 1.5:1 or 1:1 until the red blood cell transfusion threshold. There are incidences of renal dysfunction postoperatively with a restrictive fluid approach.[31,32] A multicentric Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery (RELIEF) trial also showed a high risk of renal dysfunction (8.6% vs. 5.0%, $P < 0.001$) and surgical site infection (16.5% vs. 13.6%, $P = 0.02$) in the restrictive fluid group in comparison to the liberal fluid group.[33] Haemodynamic perturbations and using nephrotoxic chemotherapeutic agents during CRS-HIPEC may increase the risk of acute kidney injury if used along with restrictive fluid therapy. In a retrospective study, though renal failure rate and peak creatinine were comparable, the length of hospital stay and 60-day postoperative complications (11.5 vs. 9.7 days, $P < 0.01$ and 28% vs. 45%, $P = 0.02$, respectively) were significantly less for restrictive fluid therapy in comparison to permissive fluid therapy.[21]

The intraoperative tissue hypoperfusion remains unrecognised with the use of static haemodynamic parameters, even with repeated measurements. SVV, PVV, systolic blood pressure variation (SPV) and CI give fluid responsiveness and guide GDFT in patients undergoing major surgery.[34] PPV, SVV and SPV are unreliable readings if the chest or the diaphragm is opened. Delta stroke volume (dSV) protocol-guided fluid therapy can be more reliable in these cases.[35] SVV was the most commonly used target for fluid therapy. Eleven studies using GDFT reported using different haemodynamic monitors such as arterial line, CVP, FloTrac, PICCO and LiDCO.[1,2,6,13,15-19,23,25] The haemodynamic targets varied across these studies. This specific value of target haemodynamic parameters may affect the amount of fluid administered and, thus, postoperative outcomes. The haemodynamic monitors are not without limitations. Their values are dependent on interpretation and also on intrathoracic pressure fluctuations. The HIPEC technique (closed vs. open abdominal technique) and its phase will also affect the interpretation of haemodynamic parameters.

The choice of choice of fluid, crystalloid versus colloid for perioperative management of major abdominal surgeries is still debatable.[36,37] The data relating to the type of fluid used for CRS-HIPEC remains inconclusive.

This systematic review has a few limitations. The included studies' study design, methodology, and outcome measures were also heterogeneous. There was no uniform GDFT protocol concerning the amount of fluid and the type of vasoactive drugs. We could not report the pooled effect as the included studies were heterogeneous regarding the interventions and outcome measures. Large-scale clinical trials are required to define the optimal amount and type of fluid for patients undergoing CRS-HIPEC procedures. Further studies are needed to evaluate different intraoperative fluid therapy regimens and haemodynamic goals.

CONCLUSION

In this systematic review, the recommendations based on available literature are not possible because studies are heterogeneous and fluid regimens and haemodynamic management are not uniform. Understanding the surgical phases, adopting an individualised approach and using a justified dynamic index cut-off to haemodynamic monitoring during the CRS-HIPEC procedure is paramount for better postoperative outcomes.

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