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Intraoperative hyperthermia is associated with increased acute kidney injury following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a retrospective cohort study

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ABSTRACT

Background: Acute kidney injury (AKI) is common after cytoreduction surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) for peritoneal surface malignancies. Herein we analyzed the association between intraoperative hyperthermia and AKI following CRS-HIPEC.

Methods: In this retrospective cohort study, we collected baseline and perioperative data from patients who underwent CRS-HIPEC mainly for pseudomyxoma peritonei between 2014 and 2020. Nasopharyngeal temperature was recorded at 5-min intervals. The area above the threshold was calculated for intraoperative hyperthermia (>37.0 °C). AKI was diagnosed and classified according to the KDIGO creatinine criteria. A multivariable logistic regression model was established to assess the association between hyperthermia and AKI.

Results: A total of 480 patients were included in the analysis. Of these, 10.6% (51/480) developed AKI within 7 postoperative days. After correction for confounding factors, a larger area above the threshold of hyperthermia was significantly associated with an increased risk of AKI (odds ratio [OR] 1.36, 95% CI 1.14–1.63, $p=0.001$). Among other factors, older age (OR 1.05, 95% CI 1.02–1.09, $p=0.002$), postoperative hypotension requiring vasopressors (OR 2.09, 95% CI 1.02–4.27, $p=0.042$), and intraperitoneal chemotherapy containing cisplatin (OR 2.75, 95% CI 1.20–6.33, $p=0.017$) were also associated with an increased risk of AKI. Patients with AKI required longer mechanical ventilation, stayed longer in the intensive care unit and hospital, developed more complications, and required more intensive care unit readmission.

Conclusions: Among patients undergoing CRS-HIPEC, intraoperative hyperthermia was independently associated with a higher risk of AKI; this effect was additive to other risk factors including cisplatin-containing chemotherapy.

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Peritoneal surface malignancies; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; acute kidney injury; postoperative complications

Background

Peritoneal surface malignancies represent a group of diseases including peritoneal carcinomatosis, pseudomyxoma peritonei, and primary peritoneal tumor, and have a significant negative influence on the prognosis [1–4]. For patients with peritoneal surface malignancies, a combined therapy including cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is recommended by the Peritoneal Surface Oncology Group International because of its benefits on long-term survival [5]. Briefly, CRS-HIPEC is an integration of surgical excision of gross tumors by multi-visceral resections and/or extensive peritonectomy, and eradication of residual tumors by intra-peritoneal irrigation with heated cytotoxic agents. Anesthetic management for patients undergoing CRS-HIPEC is complicated and challenging due to massive fluid loss and redistribution, electrolyte abnormalities, frequent intraoperative hypotension, concomitant chemotherapy, exaggerated inflammatory response, and hyperthermia and intra-abdominal hypertension secondary to the filling of perfusion fluid [6–8].

Acute kidney injury (AKI) is a common occurrence after major surgery and is associated with worse outcomes [9–12]. Potential mechanisms include ischemic insult, systemic inflammation, and nephrotoxic injury [13]. The reported incidence of AKI following CRS-HIPEC varies from 3.7 to 48.0% [14–19]. Patients with AKI after CRS-HIPEC developed more acute and chronic kidney diseases [14]; they also have higher rates of major complications, prolonged hospital stay, and increased long-term mortality [20,21]. Several risk factors

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have been identified to be associated with AKI following CRS-HIPEC, including old age, male sex, obesity, hypertension, long surgical duration, increased blood loss, intraoperative hypotension, and use of cisplatin [14,16,21–23]. Massive cytokine release and hemodynamic collapse secondary to HIPEC might also contribute [24,25]. We note that most available studies have small sample sizes, limited intraoperative covariates, and different criteria to define AKI.

Hyperthermia is harmful in some situations. For example, hyperthermia during physical work [26] and cardiopulmonary bypass rewarming are both found to be associated with AKI [27,28]. Indeed, studies reported that patients with severe hyperthermia during HIPEC developed more 30-day postoperative complications [29]. However, the effect of HIPEC-related hyperthermia on AKI development has not been clarified yet [14,22,24]. The purpose of this retrospective study was to analyze the association between intraoperative hyperthermia and the risk of AKI following CRS-HIPEC procedures.

Methods

Study design, ethics approval, and consent to participate

This was a retrospective cohort study. The protocol was approved by the Ethics Committee of Aerospace Center Hospital (No.2021-QT-014). The need for informed consent was waived by the Ethics Committee because the study was purely observational, and no patient follow-up was performed. However, all personal data were kept strictly confidential. The study was performed in accordance with the relevant guidelines and regulations.

Participants

Consecutive patients who underwent surgeries for peritoneal surface malignancies from June 2014 to December 2020 in Aerospace Center Hospital (Beijing, China) were screened. Those who were 18 years or older and underwent open or mini-invasive CRS-HIPEC procedures were included. Patients who met any of the following criteria were excluded: (1) previous chronic kidney disease (defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2) or on dialysis; (2) concomitant nephrectomy; (3) repeated CRS-HIPEC procedures (only the first procedure was included in the analysis); (4) no data of baseline creatinine (the last value before surgery during this hospitalization); (5) no data of serum creatinine during the first 7 postoperative days; (6) no data or missing data for more than 10 consecutive minutes of intraoperative nasopharyngeal temperature.

Anesthesia, procedures, and perioperative care

Standard monitoring included electrocardiogram, invasive arterial blood pressure, pulse oxygen saturation, end-tidal carbon dioxide, inhalational anesthetics, nasopharyngeal temperature, and urine output [30]. Central venous pressure and cardiac output were monitored when considered necessary. Arterial blood gas was monitored periodically throughout the procedure.

General anesthesia was performed for all patients using propofol, volatile anesthetic (mainly sevoflurane), and opioids, in combination with muscle relaxants. Fluid therapy included a continuous baseline infusion of crystalloids. Artificial (gelatin) and/or natural colloids (albumin) were infused for volume replacement. Blood products were transfused to maintain hemoglobin concentration higher than 7 g/dL. Vasopressors were applied to keep blood pressure within 30% from baseline, at the discretion of anesthesiologists. Urinary output was maintained at least 0.5 mL/kg/h but usually higher; diuretics were administered after excluding hypoperfusion. Intraoperative body temperature was maintained according to the local routine, including the use of an underbody warming blanket to prevent hypothermia during the CRS phase, which was turned off about 30 min before HIPEC, and the use of ice packs around the head and neck to prevent hyperthermia during the HIPEC phase.

CRS as described by Sugarbaker [31] was performed according to the clinical judgment of the attending surgeons. Following CRS, intraoperative HIPEC was performed using a closed-abdomen technique. Specifically, four catheters (two inflow and two outflow) were placed into the abdominal cavity before temporary closure of the abdominal wall. The catheters were then connected to a perfusion machine for hyperthermic chemotherapy (RHL-2000B, Jilin Maida Technology Development Co., Ltd., Jilin, China); the machine heated and circulated the perfusion fluid with an inflow temperature of 43.5 °C and an outflow temperature of about 42.0 °C. Chemotherapeutics mainly included cisplatin (50–90 mg), 5-fluorouracil (1 g), and mitomycin C (10–40 mg). The volume of perfusate was decided according to the abdominal cavity volume and the Chinese Expert Consensus [32]. The perfusion rate was controlled at 600–1000 mL/min, and perfusion duration was typically 60 min for cisplatin and 90 min for 5-fluorouracil or other regimens. After HIPEC, the abdominal cavity was reopened for digestive tract reconstruction, drainage tube placement, and sufficient hemostasis, and then reclosed.

After surgery, patients who were stable following an uneventful procedure were transferred to the general wards; otherwise, they were admitted to the intensive care unit (ICU) for further monitoring and treatment. A patient-controlled intravenous analgesia pump was provided for postoperative analgesia. Early postoperative intraperitoneal chemotherapy was typically conducted using 5-fluorouracil (1 g), with or without cisplatin (40–100 mg) or raltitrexed (4 or 5 mg), from postoperative days 2 to 6 as appropriate, according to the Chinese expert consensus [32] and clinical judgment of the attending surgeons. Other perioperative management was performed according to the local routine.

Data collection and outcomes

Baseline data included demographics (age, sex, body mass index), preoperative comorbidities and medications, history

of previous therapy (surgery, systemic and/or intraperitoneal chemotherapy, and blood transfusion), general status (American Society of Anesthesiologist classification, Charlson Comorbidity Index [33]), preoperative laboratory tests, and tumor characteristics (final diagnosis, tumor origin, and histopathology). Histopathology of pseudomyxoma peritonei was classified according to the 2016 Peritoneal Surface Oncology Group International consensus and included disseminated peritoneal adeno-mucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S) [34].

Anesthesia-related data were collected from the anesthesia information management system (Suzhou Medical System Technology Co., Ltd., Jiangsu, China). Nasopharyngeal temperature was monitored continuously during surgery (Shenzhen Mindray Bio-medical Electronics Co., Ltd., Guangdong, China) and was automatically captured and stored at a 5-min interval. The recorded temperature was unmodifiable. After collecting temperature information, we identified and removed monitoring artifacts according to the following rules, i.e., temperature readings documented as artifacts, temperature readings out of a predefined range (≤30.0 °C), and abrupt changes (≥0.4 °C) between two neighboring measurements. Invalid temperature reading between measurements was linearly interpolated. Other data including mean arterial pressure, medications, and fluid balance during anesthesia were also recorded.

Surgery-related data were collected from the inpatient medical record system. The peritoneal cancer index was used to quantify the peritoneal tumor burden during surgical exploration. The index evaluated 13 abdominopelvic regions; each region was scored from 0 to 3, resulting in a total score from 0 to 39; higher score indicated higher tumor burden [35]. The completeness of cytoreduction was used to evaluate the volume of residual cancer after surgery: grade 0 indicated no macroscopic residual cancer nodule remained; grade 1 no nodule >2.5 mm in diameter remained; grade 2 nodule between 2.5 mm and 2.5 cm in diameter remained; and grade 3 nodule >2.5 cm in diameter remained. Complete cytoreduction indicated grades 0 or 1 after CRS [35]. Other perioperative information included duration of surgery, use of ureteral stent, intraoperative HIPEC, types of antibiotics, postoperative use of vasopressors, and postoperative intraperitoneal chemotherapy within 6 days.

Our primary outcome was the occurrence of AKI which was diagnosed according to the Kidney Disease Improving Global Outcome (KDIGO) creatinine criteria [36] within 7 days after surgery. Specifically, patients were considered to have AKI if the postoperative serum creatinine value increased either by ≥0.3 mg/dL within 48 h, or 1.5 times baseline within 7 days after surgery. The severity of AKI was also classified according to the KDIGO criteria. Stage 1 refers to serum creatinine increase by ≥0.3 mg/dL or 1.5–1.9 times baseline; stage 2 refers to increase in creatinine 2–2.9 times baseline; stage 3 refers to increase in creatinine by ≥4 mg/dL or 3 times baseline, or initiation of renal replacement therapy [36].

Secondary outcomes included intensive care unit (ICU) admission, occurrence and grades of complications within 30 days, and hospital stay after surgery. For those who were admitted to the ICU, duration of mechanical ventilation and length of ICU stay were recorded. Postoperative complications were defined as new-onset conditions that were harmful for patients' recovery and required therapeutic intervention, i.e., grade 2 or higher on Clavien-Dindo classification [37]. For patients who developed multiple complications, only the most severe one was taken into analysis.

Statistical analysis

To reflect the fluctuation of nasopharyngeal temperature, the area above the threshold was calculated for intraoperative hyperthermia (>37.0 °C), and the area under the threshold was calculated for intraoperative hypothermia (<37.0 °C). Calculations were performed by summarizing all areas ($a_1 + a_2 + a_3 \ldots$) above/below the given thresholds during the whole procedure; each area was calculated with the use of the trapezoid rule and linear interpolation between neighboring measurements. We also calculated the area above the threshold after initiating HIPEC. Python 3.10 software was used for the calculation.

Patients were analyzed in two groups, i.e., those who developed AKI and those who did not. Continuous data with normal distribution (according to the Kolmogorov-Smirnov test) were compared with Student's *t*-test; otherwise, the Mann–Whitney *U* test was used. Categorical data were compared with chi-square test, chi-square test with continuity correction, or Fisher exact test. Time-to-event variables were analyzed with Kaplan–Meier survival estimators, between group differences were compared with log-rank tests.

To find out the correlation between year of surgery and categorical variable (use of cisplatin and incidence of AKI), chi-square trend test was used; the correlation between year of surgery and continuous variable (average area above 37.0 °C) was tested using One-Way ANOVA.

To identify factors in association with AKI, variables with *p*-values <0.20 in univariable logistic regression analyses (excluding those correlated with others) or were considered clinically important, together with area above threshold reflecting intraoperative hyperthermia, were included in a multivariable model with backward stepwise elimination.

As sensitivity analyses, we performed multivariable regressions after replacing the area above threshold >37 °C during the whole procedure with the area above threshold >37 °C after initiating HIPEC, after excluding patients who underwent surgery in the year 2018 during which period missing temperature data frequently occurred, or after including history of hypertension and use of gelatin during surgery. We also performed stepwise regressions based on variables screened by Boruta algorithm, lasso regression, and lasso regression combined with a decision tree model, to further test the association between intraoperative hyperthermia and the risk AKI after CRS-HIPEC.

A p-value <0.05 was considered statistically significant. All analyses were performed with the use of SPSS 26.0 Statistics software (IBM SPSS, Inc., Chicago, IL, USA) and R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between 1 June 2014 and 30 December 2020, 782 patients underwent CRS-HIPEC procedures. Among them, 231 patients were excluded due to no intraoperative temperature recording (mainly among those who underwent surgery in the year 2018 due to an update of the anesthesia information system), 37 were excluded due to repeated CRS-HIPEC procedures (only the first combined procedure was used for analysis), 32 were excluded due to no serum creatinine data, and two were excluded due to concomitant nephrectomy. At last, 480 patients (mean age 57 years; 36.9% male; median peritoneal cancer index 27 [interquartile range 19–32]) were included in the final analysis (Supplement Figure S1).

Of the included patients, 89.6% (430/480) were diagnosed as pseudomyxoma peritonei, 80.0% (384/480) had tumor originated from the appendix, 38.3% (184/480) achieved completed cytoreduction (grades 0 and 1), 73.1% (351/480) received early postoperative intraperitoneal chemotherapy, 60.8% (292/480) received cisplatin-containing chemotherapy, and 10.6% (51/480) developed AKI during the first 7 postoperative days. When compared with patients who did not develop AKI, those who developed AKI were older (60 ± 9 *vs.* 56 ± 11 years, $p = 0.039$), had more comorbid hypertension (41.2% [21/51] *vs.* 24% [103/429], $p = 0.008$), had less pseudomyxoma peritonei (76.5% [39/51] *vs.* 91.1% [391/429], $p = 0.001$) and less appendiceal origin (66.7% [34/51] *vs.* 81.6% [350/429], $p = 0.012$), underwent longer surgery (median 9.3 h [interquartile range 7.4–11.0] *vs.* 7.8 h [6.5–9.4], $p = 0.001$), endured more severe intraoperative hyperthermia (area above threshold of >37.0 °C, 153.3 °C × min [85.9–225.1] *vs.* 89.1 °C × min [31.3–160.8], $p < 0.001$), required more vasopressors for hypotension after surgery (29.4% [15/51] *vs.* 14.0% [60/429], $p = 0.004$), and received less intraperitoneal chemotherapy after surgery (58.8% [30/51] *vs.* 74.8% [321/429], $p = 0.015$) but more cisplatin-containing intraperitoneal chemotherapy during the perioperative period (84.3% [43/51] *vs.* 58.0% [249/429], $p < 0.001$; Tables 1 and 2; Supplement Tables S1 and S2).

Of patients who developed postoperative AKI, 84.2% (42/51) had stage 1, 15.7% (8/51) had stage 2, and 2.0% (1/51) had stage 3 AKI; none of them required renal replacement therapy. When compared with patients who did not develop AKI, those who developed AKI required more ICU readmission (7.8% [4/51] *vs.* 1.9% [8/429], $p = 0.035$), stayed longer on mechanical ventilation (8 h [4–13] *vs.* 5 h [3–9], $p = 0.014$) and

Table 1. Baseline data.

	Total ($n = 480$)	No AKI ($n = 429$)	AKI ($n = 51$)	p-Value
Demographic data				
Age, year	57 ± 11	56 ± 11	60 ± 9	**0.039**
Male sex	177 (36.9%)	157 (36.6%)	20 (39.2%)	0.714
Body mass index, kg/m^2	23.1 (20.8, 25.7)	23.1 (21.0, 25.6)	23.0 (20.8, 26.3)	0.735
Comorbidity				
Hypertension	124 (25.8%)	103 (24.0%)	21 (41.2%)	**0.008**
Diabetes	50 (10.4%)	41 (9.6%)	9 (17.6%)	0.074
Coronary heart disease	20 (4.2%)	15 (3.5%)	5 (9.8%)	0.078
Other cardiac diseases[a]	14 (2.9%)	13 (3.0%)	1 (2.0%)	>0.999
Hyper-/hypothyroidism	15 (3.1%)	13 (3.0%)	2 (3.9%)	>0.999
Chronic hepatic dysfunction[b]	15 (3.1%)	12 (2.8%)	3 (5.9%)	0.440
Chronic smoking[c]	7 (1.5%)	6 (1.4%)	1 (2.0%)	0.547
History of therapy				
Previous surgery	362 (75.4%)	323 (75.3%)	39 (76.5%)	0.853
Systemic/intraperitoneal chemotherapy	196 (40.8%)	171 (39.9%)	25 (49.0%)	0.208
Blood transfusion	22 (4.6%)	17 (4.0%)	5 (9.8%)	0.126
General status				
ASA physical status				0.077
I–II	235 (49.0%)	216 (50.3%)	19 (37.3%)	
III–IV	245 (51.0%)	213 (49.7%)	32 (62.7%)	
Charlson comorbidity index, point	8 (8, 8)	8 (8, 8)	8 (8, 8)	0.398
Last laboratory tests				
Albumin, g/L	36 ± 4	36 ± 4	36 ± 4	0.436
Hemoglobin, g/L	114.4 ± 18.2	114.5 ± 17.7	113.0 ± 22.4	0.658
Creatinine, μmol/L	63.0 ± 17.6	62.6 ± 14.3	66.2 ± 33.9	0.472
Tumor characteristics				
Type of histopathology[d]				**0.001**
Pseudomyxoma peritonei	430 (89.6%)	391 (91.1%)	39 (76.5%)	
Non-pseudomyxoma peritonei	50 (10.4%)	38 (8.9%)	12 (23.5%)	
Appendiceal origin	384 (80.0%)	350 (81.6%)	34 (66.7%)	**0.012**

AKI: acute kidney injury; ASA: American Society of Anesthesiologists.
Data are mean ± *SD*, median (interquartile range), or *n* (%). *p*-Values in bold indicate <0.05.
[a]Included valvular heart disease, atrial fibrillation, frequent or multifocal premature ventricular contraction, atrioventricular block, and tachycardia.
[b]Defined as Child-Pugh classes B and C.
[c]Indicated smoking of cigarettes more than half a pack per day for at least 2 years.
[d]Also see Supplement Table S1.

Table 2. Intra- and postoperative data.

	Total ($n=480$)	No AKI ($n=429$)	AKI ($n=51$)	p-Value
Surgery-related data				
Peritoneal cancer index, point[a]	27 (19, 32)	27 (18, 32)	28 (21, 32)	0.478
Duration of surgery, h	8.0 (6.5, 9.6)	7.8 (6.5, 9.4)	9.3 (7.4, 11.0)	**0.001**
Use of ureteral stent	166 (34.6%)	144 (33.6%)	22 (43.1%)	0.174
Grade of cytoreduction[b]				0.124
Grade 0	73 (15.2%)	69 (16.1%)	4 (7.8%)	
Grade 1	111 (23.1%)	94 (21.9%)	17 (33.3%)	
Grade 2	135 (28.1%)	123 (28.7%)	12 (23.5%)	
Grade 3	153 (31.9%)	137 (31.9%)	16 (31.4%)	
Unknown	8 (1.7%)	6 (1.4%)	2 (3.9%)	
Complete cytoreduction[c]	184 (38.3%)	163 (38.0%)	21 (41.2%)	0.659
Intraoperative care				
Crystalloid, mL	3300 (2700, 4200)	3300 (2700, 4200)	3600 (2800, 4400)	0.254
Gelatin, mL	2600 (2000, 3200)	2600 (2000, 3200)	2700 (1700, 3600)	0.278
20% albumin, mL	100 (100, 200)	100 (100, 175)	100 (100, 200)	0.062
Blood transfusion	295 (61.5%)	262 (61.1%)	33 (64.7%)	0.614
Use of vasopressors	355 (74.0%)	319 (74.4%)	36 (70.6%)	0.562
Use of diuretics	268 (55.8%)	233 (54.3%)	35 (68.6%)	0.052
Estimated blood loss, mL	1500 (800, 1800)	1500 (800, 1600)	1500 (800, 2000)	0.372
Urine output, mL	1000 (800, 1500)	1000 (800, 1500)	1000 (800, 1500)	0.711
Highest lactate, mmol/L	2.2 (1.3, 3.3)	2.2 (1.3, 3.3)	2.1 (1.4, 3.3)	0.842
Lowest hematocrit, %	20 (17, 24)	21 (17, 24)	19 (16, 24)	0.138
MAP, mmHg	73 (69, 77)	73 (69, 77)	73 (69, 78)	0.506
Administration of HIPEC[d]	480 (100.0%)	429 (100.0%)	51 (100.0%)	—
Area above threshold (°C × min)				
>38.0	7.9 (0.0, 43.0)	6.0 (0.0, 39.4)	36.8 (1.0, 79.3)	**<0.001**
>37.5	40.9 (2.3, 98.0)	35.5 (1.6, 90.5)	84.5 (29.6, 138.7)	**<0.001**
>37.0	94.1 (33.4, 168.9)	89.1 (31.3, 160.8)	153.3 (85.9, 225.1)	**<0.001**
Area under threshold (°C × min)				
<37.0	323.6 (181.4, 501.8)	325.6 (185.2, 501.0)	288.4 (145.1, 556.6)	0.727
<36.5	148.8 (46.2, 300.0)	151.7 (48.1, 298.3)	124.8 (18.3, 316.8)	0.490
<36.0	25.4 (0.0, 120.5)	27.0 (0.0, 120.9)	12.0 (0.0, 129.0)	0.447
Postoperative data				
Hypotension requiring vasopressors[e]	75 (15.6%)	60 (14.0%)	15 (29.4%)	**0.004**
Type of antibiotics				
Carbapenems[f]	175 (36.5%)	153 (35.7%)	22 (43.1%)	0.295
Cephalosporins[g]	184 (38.3%)	163 (38.0%)	21 (41.2%)	0.659
Nitroimidazoles[h]	82 (17.1%)	74 (17.2%)	8 (15.7%)	0.779
Others[i]	108 (22.5%)	100 (23.3%)	8 (15.7%)	0.218
Intraperitoneal chemotherapy[d]	351 (73.1%)	321 (74.8%)	30 (58.8%)	**0.015**
Perioperative data				
Intraperitoneal chemotherapy[j]				
5-Fluorouracil	397 (82.7%)	363 (84.6%)	34 (66.7%)	**0.001**
Cisplatin	292 (60.8%)	249 (58.0%)	43 (84.3%)	**<0.001**
Mitomycin C	190 (39.6%)	183 (42.7%)	7 (13.7%)	**<0.001**
Raltitrexed	54 (11.3%)	48 (11.2%)	6 (11.8%)	0.902
Combination of intraperitoneal chemotherapy				**<0.001**
None-cisplatin[k]	188 (39.2%)	180 (42.0%)	8 (15.7%)	
Cisplatin only	81 (16.9%)	64 (14.9%)	17 (33.3%)	
Cisplatin plus one[l]	149 (31.0%)	129 (30.1%)	20 (39.2%)	
Cisplatin plus two[m]	62 (12.9%)	56 (13.1%)	6 (11.8%)	

AKI: acute kidney injury; MAP: mean arterial pressure; HIPEC: hyperthermic intraperitoneal chemotherapy.
Data are median (interquartile range) or n (%). p-Values in bold indicate <0.05.
[a]Used to quantify peritoneal tumor burden before surgery; score ranges from 0 to 39, with higher score indicating higher tumor burden [35].
[b]Grade 0: no macroscopic residual nodule; grade 1: residual nodule ≤2.5 mm; grade 2: residual nodule >2.5 mm but ≤2.5 cm; and grade 3: residual nodule ≥2.5 cm [35].
[c]Included cytoreduction grade 0 and grade 1 [35].
[d]Also see Supplement Table S2.
[e]Included norepinephrine (52 cases), dopamine (4 cases), norepinephrine combined with dopamine (2 cases), metaraminol (14 cases), and desmopressin (3 cases).
[f]Included ertapenem (163 cases) and imipenem-cilastatin (12 cases).
[g]Included cefazolin (90 cases), cefoxitin (73 cases), ceftizoxime (13 cases), cefmetazole (5 cases), and cefoperazone (3 cases).
[h]Included ornidazole (39 cases), tinidazole (34 cases), and metronidazole (9 cases).
[i]Included latamoxef (96 cases), levofloxacin (7 cases), and piperacillin (5 cases).
[j]Included those administered intraoperatively and up to 6 days after surgery. Also see Supplement Table S2.
[k]Included 5-fluorouracil only (7 cases), mitomycin C only (1 case), and 5-fluorouracil + mitomycin C (180 cases).
[l]Included cisplatin + 5-fluorouracil (148 cases) and cisplatin + raltitrexed (1 case).
[m]Included cisplatin + 5-fluorouracil + mitomycin C (9 cases) and cisplatin + 5-fluorouracil + raltitrexed (53 cases).

in ICU (16 h [14–18] *vs.* 15 h [14–17], $p=0.038$), developed more major complications (47.1% [24/51] *vs.* 29.4% [126/429], $p=0.010$) and higher grade complications (≥grade 4: 17.6% [9/51] *vs.* 4.4% [19/429], $p<0.001$), and stayed longer in hospital after surgery (17 days [15–23] *vs.* 16 days [14–20], $p=0.001$; Figure 1; Table 3; Supplement Table S3).

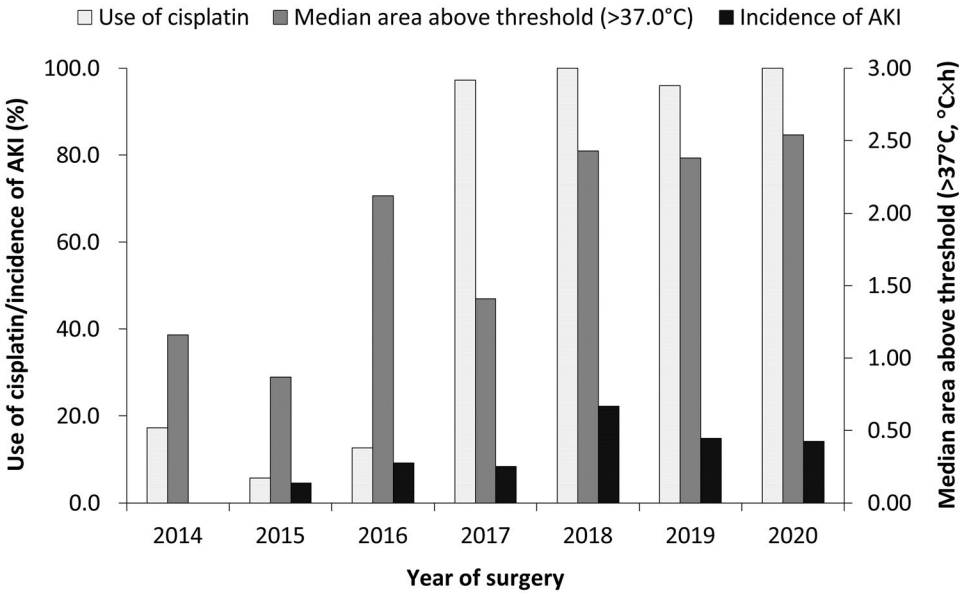

Figure 1. Use of cisplatin, intraoperative hyperthermia, and occurrence of AKI across the study period. Both cisplatin usage during intraperitoneal chemotherapy (p for trend <0.001) and median area above the threshold of hyperthermia (>37 °C; p for trend <0.001) increased significantly along with time, so was the incidence of AKI (p for trend =0.001) after surgery. AKI: acute kidney injury.

Table 3. Postoperative outcomes.

	Total (n = 480)	No AKI (n = 429)	AKI (n = 51)	p-Value
Acute kidney injury[a]	51 (10.6%)	0 (0.0%)	51 (100.0%)	**<0.001**
Grade 1	42 (8.8%)	0 (0.0%)	42 (82.4%)	
Grade 2	8 (1.7%)	0 (0.0%)	8 (15.7%)	
Grade 3	1 (0.2%)	0 (0.0%)	1 (2.0%)	
ICU admission	334 (69.6%)	293 (68.3%)	41 (80.4%)	0.076
With intubation	331 (69.0%)	290 (67.6%)	41 (80.4%)	0.062
Duration of MV, h[b]	5 (3, 10)	5 (3, 9)	8 (4, 13)	**0.014**
Length of ICU stay, h	15 (14, 17)	15 (14, 17)	16 (14, 18)	**0.038**
Repeat ICU admission	12 (2.5%)	8 (1.9%)	4 (7.8%)	**0.035**
Other complications[c]	150 (31.3%)	126 (29.4%)	24 (47.1%)	**0.010**
Neurological complications	3 (0.6%)	3 (0.7%)	0 (0.0%)	>0.999
Acute hepatic injury	36 (7.5%)	30 (7.0%)	6 (11.8%)	0.346
Respiratory complications	34 (7.1%)	27 (6.3%)	7 (13.7%)	0.095
Circulatory complications	48 (10.0%)	36 (8.4%)	12 (23.5%)	**0.001**
Surgical complications	63 (13.1%)	52 (12.1%)	11 (21.6%)	0.059
Thrombosis/embolism	20 (4.2%)	17 (4.0%)	3 (5.9%)	0.781
Surgical infection	20 (4.2%)	15(3.5%)	5 (9.8%)	0.078
Others	1 (0.2%)	1 (0.2%)	0 (0.0%)	>0.999
Grade of complications[d]				**0.002**
Grade 0/1	330 (68.8%)	303 (70.6%)	27 (52.9%)	
Grade 2	89 (18.5%)	79 (18.4%)	10 (19.6%)	
Grade 3	31 (6.5%)	27 (6.3%)	4 (7.8%)	
Grade 4	28 (5.8%)	19 (4.4%)	9 (17.6%)	
Grade 5	2 (0.4%)	1 (0.2%)	1 (2.0%)	
Hospital stay after surgery, day	17 (14, 20)	16 (14, 20)	17 (15, 23)	**0.001**

AKI: acute kidney injury; ICU: intensive care unit; MV: mechanical ventilation.
Data are n (%) or median (interquartile range). p-Values in bold indicate <0.05.
[a]According to Kidney Disease Improving Global Outcome creatinine criteria [36].
[b]Results of patients with endotracheal intubation.
[c]Indicated Clavien-Dindo grade 2 or higher. Also see Supplement Table S3.
[d]According to Clavien-Dindo classification [37]. Excluded acute kidney injury.

Univariable analyses identified 22 factors with p < 0.20 in association with AKI development (Supplement Table S4). After excluding factors that had a correlation with others, 12 factors including area above the threshold of >37.0 °C were included in a multivariable regression model. After correction for confounding factors, larger area above the threshold of >37.0 °C was independently associated with an increased risk of AKI (odds ratio [OR] 1.36, 95% CI 1.14–1.63, p = 0.001). Among other factors, older age (OR 1.05, 95% CI 1.02–1.09, p = 0.002), postoperative hypotension requiring vasopressors (OR 2.09, 95% CI 1.02–4.27, p = 0.042), and intraperitoneal chemotherapy containing cisplatin (OR 2.75, 95% CI 1.20–6.33, p = 0.017) were also associated with an increased risk of AKI (Table 4).

Table 4. Risk factors associated with acute kidney injury.

	Univariable regression		Multivariable regression[a]	
Variables	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Area above threshold of 37.0 °C during surgery, per °C × h	1.38 (1.19, 1.61)	**<0.001**	1.36 (1.14, 1.63)	**0.001**
Age, year	1.03 (1.00, 1.06)	**0.040**	1.05 (1.02, 1.09)	**0.002**
ASA physical status				
I–II	Reference		—	—
III–IV	1.71 (0.94, 3.11)	0.080	—	—
Preoperative blood transfusion	2.63 (0.93, 7.44)	0.069	—	—
Preoperative creatinine, μmol/L	1.01 (0.99, 1.02)	0.198	—	—
Histopathology of tumor[b]				
Non-pseudomyxoma peritonei	Reference		—	—
Pseudomyxoma peritonei	0.31 (0.15, 0.65)	**0.002**	—	—
Duration of surgery, hour	1.24 (1.08, 1.42)	**0.002**	—	—
Use of ureteral stent	1.50 (0.83, 2.71)	0.176	—	—
20% albumin, per 50 mL	1.24 (0.98, 1.57)	0.076	—	—
Use of diuretics	1.84 (0.99, 3.43)	0.054	—	—
Postoperative hypotension requiring vasopressors[c]	2.56 (1.32, 4.96)	**0.005**	2.09 (1.02, 4.27)	**0.042**
Intraperitoneal chemotherapy[d]				
Non-cisplatin containing[e]	Reference		Reference	
Cisplatin containing[f]	3.88 (1.78, 8.46)	**0.001**	2.75 (1.20, 6.33)	**0.017**

OR: odds ratio; CI: confidence interval; ASA: American Society of Anesthesiologists.
p-Values in bold indicate <0.05.
[a]With backward stepwise elimination. Hosmer-Lemeshow goodness-of-fit test: $\chi^2 = 9.950$, $df = 8$, $p = 0.269$. Also see Supplement Table S4 for univariable analyses.
[b]See Supplement Table S1 for details.
[c]Included norepinephrine (52 cases), dopamine (4 cases), norepinephrine combined with dopamine (2 cases), metaraminol (14 cases), and desmopressin (3 cases).
[d]Included intraoperative therapy and postoperative therapy within six days.
[e]Included 5-fluorouracil only (7 cases), mitomycin C only (1 case), and 5-fluorouracil + mitomycin C (180 cases).
[f]Included cisplatin only (81 cases) and cisplatin + others (211 cases).

Sensitivity analyses did not change our conclusions. Intraoperative hyperthermia remained a factor that was independently associated with an increased risk of AKI in the multivariable regression models after replacing the area above threshold >37 °C during the whole procedure with the area above threshold >37 °C after initiating HIPEC (OR 1.31, 95% CI 1.06–1.61, $p = 0.010$; Supplement Tables S5), excluding patients who underwent surgery in the year 2018 (OR 1.50, 95% CI 1.24–1.82, $p < 0.001$; Supplement Tables S6), or including history of hypertension and gelatin use during surgery (OR 1.44, 95% CI 1.21–1.71, $p < 0.001$; Supplement Tables S7), and in stepwise regression models based on variables screened by Boruta algorithm (OR 1.30, 95% CI 1.11–1.53, $p = 0.001$; Supplement Tables S8 and S9), lasso regression (OR 1.01, 95% CI 1.00–1.01, $p < 0.001$; Supplement Figure S2; Supplement Tables S10), and a combination of lasso regression and decision tree model (OR 1.02, 95% CI 1.00–1.03, $p = 0.021$; Supplement Figure S3; Supplement Tables S11).

Discussion

In this study, we retrospectively analyzed 480 patients who were treated with CRS-HIPEC mainly for pseudomyxoma peritonei; 10.6% of them developed AKI after surgery. We found that intraoperative hyperthermia was significantly correlated with the occurrence of AKI; that is, a larger area above the threshold of hyperthermia was associated with a higher risk of AKI. The nephrotoxic effect of intraoperative hyperthermia was additive to that of other risk factors including old age, use of vasopressors after surgery, and use of cisplatin-containing chemotherapy.

Hyperthermic intraperitoneal chemotherapy, usually in combination with cytoreductive surgery, has been successfully used in patients with peritoneal surface malignancies [38,39]. The therapy is associated with organ-specific adverse events including AKI [15–19,40]. Traditionally, AKI following CRS-HIPEC was mainly attributed to nephrotoxicity of chemotherapeutic agents (especially cisplatin-containing regimen), whereas the effect of hyperthermia during HIPEC remains to be determined [22,24]. In other situations, such as physical work in hot environment and cardiac surgery with cardiopulmonary bypass, the potential nephrotoxic effect of hyperthermia had been reported [26–28]. In the present study, we defined intraoperative hyperthermia as nasopharyngeal temperature >37.0 °C. Our results confirmed the nephrotoxic effect of hyperthermia which was additive to that of other factors including cisplatin.

The potential mechanisms underlying our findings are not totally clear but may include the following. First, heat-induced sweating may lead to decreased extracellular fluid and dehydration [41]; the subsequently decreased blood volume may render less blood being filtrated by the kidney, resulting in a decreased glomerular filtration rate and consequently leading to AKI [42]. Second, dehydration induced by heat exposure stimulates vasopressin secretion which may adversely affect renal circulation and result in tubular and glomerular injury [43]. Third, heat exposure may lead to oxidative stress and inflammation, and subsequent renal injury [44,45]. Although the pathophysiology of heat ambient-relative AKI is clear and plausible, data demonstrating links between short-term intraoperative hyperthermia and AKI after CRS-HIPEC were sparse and complicated by other

confounding variables (such as surgery, exposure to cisplatin, etc.). It is necessary to further investigate the potential impact of short-term intraoperative hyperthermia on AKI after CRS-HIPEC and the underlying mechanisms.

Previous studies have identified cisplatin as an important risk factor for HIPEC-related AKI [22,46]. To date, the extent of direct nephrotoxic effects that cisplatin contributes to AKI development following CRS-HIPEC remained controversial [15,24]. The nephrotoxicity of cisplatin is dose-dependent [47–50]; however, the plasma levels of cisplatin during HIPEC are well below the cytotoxic threshold [51]. Therefore, the direct nephrotoxicity of cisplatin is not sufficient to explain the AKI incidence observed after CRS-HIPEC [17,52]. Both *in vitro* and *in vivo* studies showed that cisplatin's pharmacokinetics are changed, and anti-cancer effect is enhanced by the concomitant hyperthermia [53,54]. Our results suggest that cisplatin's nephrotoxicity is also potentiated in the context of hyperthermia. More studies are required to confirm our hypothesis.

Aging is associated with a decline in renal blood flow and glomerular filtration rate [55]. Hence, it was not surprising that old age was associated with AKI in our cohort. Previous studies found that postoperative hypotension is common and associated with an increased risk of adverse cardiac and cerebrovascular events [56,57]. Our results suggest that postoperative use of vasopressors for hypotension during ICU stay after surgery was also associated with an increased risk of AKI. Consistent with others [20,21,58], we found that patients who developed AKI had prolonged ICU and hospital stay, longer mechanical ventilation duration, more ICU readmission, and higher rates of major complications. Measures that provide effective nephroprotection may reduce renal complications and improve perioperative recovery. In this respect, adequate perioperative fluid and cytoprotection with amifostine and sodium thiosulfate might be helpful but require further demonstration [59–61].

The strengths of this study include that we included a relatively large sample size and calculated the area under/above thresholds to evaluate the magnitude and duration of intraoperative temperature fluctuation. There are some limitations in addition to the retrospective nature. First, 29.5% (231/782) of screened patients were excluded from analysis due to missing intraoperative temperature. However, the temperature data missing was due to technical reasons (update of the anesthesia information system) and mainly occurred in the year 2018. Sensitivity analysis after excluding all patients who underwent surgery in the year 2018 (45 cases) did not change our conclusions. Second, we diagnosed AKI only according to serum creatinine concentrations and thus might have underestimated the occurrence of AKI after surgery. Furthermore, 4.1% (32/782) of screened patients were excluded from analysis due to no postoperative creatinine measurements; this might also produce bias although acceptable. Third, in this single-center study, most enrolled patients were diagnosed as pseudomyxoma peritonei; potential pharmacological nephroprotection, such as amifostine [59] or sodium thiosulfate [60] was not provided. These limited the generalizability of our results.

Conclusions

Our results showed that among patients undergoing CRS-HIPEC, intraoperative hyperthermia was associated with an increased risk of AKI. The nephrotoxic effect of intraoperative hyperthermia was additive to that of other risk factors including cisplatin-containing intraperitoneal chemotherapy. Future studies are required to explore kidney protective strategies in this patient population.

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Consent for publication

Not applicable.

Authors contributions

SCG designed the study, collected, analyzed, and interpreted the data, and drafted the manuscript. JHM contributed to data analysis. HK contributed to the study conception. RQM and SLC contributed to data collection. DXW conceived and designed the study, reviewed the original data and the results of analyses, and critically revised the manuscript. All authors read and approved the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets generated and analyzed during the current study are not publicly available due to institutional restrictions but are available from the corresponding author upon reasonable request.

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