Acute kidney injury after cytoreductive surgery and hyperthermic intraoperative cisplatin chemotherapy for malignant pleural mesothelioma

Tammy Hod, MD,[a] Katherin J. Freedberg, AB,[a] Shveta S. Motwani, MD,[a,b] Margaret Chen, BS,[a] Gyorgy Frendl, MD, PhD,[c] David E. Leaf, MD, MMSC,[a] Shruti Gupta, MD, MPH,[a] Suraj Sarvode Mothi, MPH,[a] William G. Richards, PhD,[d] Raphael Bueno, MD,[d] and Sushrut S. Waikar, MD, MPH[a,e]

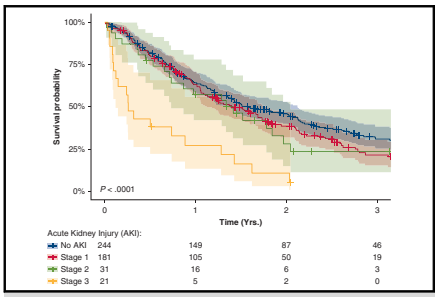
ABSTRACT

Objectives: Cytoreductive surgery with hyperthermic intraoperative chemotherapy with cisplatin has been used successfully to treat malignant pleural mesothelioma, a highly aggressive malignancy that is rapidly fatal in most cases. We hypothesized that the combination of ischemic injury with nephrotoxic injury from cisplatin would result in high rates of acute kidney injury.

Methods: We conducted an observational study in 503 patients to study the risks and outcomes of acute kidney injury after surgical resection of malignant pleural mesothelioma. Eligible subjects underwent extrapleural pneumonectomy or pleurectomy/decortication with or without hyperthermic intraoperative chemotherapy. Acute kidney injury was defined as an increase in creatinine of 26.5 μmol/L or greater within 48 hours of surgery or a 50% or greater increase over 7 days.

Results: Acute kidney injury developed in 243 patients (48.3%). Severe acute kidney injury requiring renal replacement therapy developed in 16 patients (3.2%). Major significant predictors for acute kidney injury included male sex (odds ratio, 2.98; $P < .001$), intraoperative cisplatin administration (odds ratio, 3.12; $P < .001$), previous cisplatin exposure (odds ratio, 1.96; $P = .02$), hypertension (odds ratio, 1.57; $P = .02$), and longer surgical time (odds ratio, 1.15 per hour; $P = .02$). Compared with patients without acute kidney injury, those with severe acute kidney injury had longer length of stay (26 vs 13 days) and a 2.71-fold increased risk of death in multivariable-adjusted models.

Conclusions: Acute kidney injury is common after cytoreductive surgery with hyperthermic intraoperative chemotherapy with cisplatin and is associated with poor long-term outcomes. Strategies to prevent postoperative acute kidney injury are needed to improve multimodal treatment of malignant pleural mesothelioma. (J Thorac Cardiovasc Surg 2021;161:1510-8)



Long-term mortality in those who did or did not develop AKI.

CENTRAL MESSAGE

AKI is common after cytoreductive surgery with intrathoracic cisplatin for MPM and is associated with poor long-term outcomes.

PERSPECTIVE

Cytoreductive surgery with HIOC with cisplatin has been used successfully to treat MPM. AKI is a common complication after this procedure. We identified risk factors that may help clinicians who are counseling patients about their individual risks of postoperative complications.

See Commentaries on pages 1519, 1520, and 1522.

Malignant pleural mesothelioma (MPM) is a rare but highly aggressive malignancy of the pleura that is rapidly fatal in most cases. Median survival in patients treated with standard of care chemotherapy (pemetrexed and cisplatin) is approximately 12 months.[1] Extended median survival of 18 to 23 months has been observed in some reports with multimodality protocols that include a combination of cytoreductive surgery, systemic chemotherapy, and radiotherapy.[2,3] Selection for each treatment modality is determined on the basis of a patient's stage and histologic type, competing comorbidities, and personal preference for aggressive treatment. Unfortunately, locoregional

From the [a]Division of Renal Medicine, [c]Department of Anesthesiology, Perioperative and Pain Medicine, and [d]Department of Surgery, Division of Thoracic Surgery, Brigham and Women's Hospital, Boston, Mass; [b]Adult Survivorship Program, Dana-Farber Cancer Institute, Boston, Mass; and [e]Section of Nephrology, Department of Medicine, Boston University School of Medicine and Boston Medical Center, Boston, Mass.

T. Hod and K.J. Freedberg are co-first authors.

Received for publication July 31, 2019; revisions received May 6, 2020; accepted for publication May 11, 2020; available ahead of print May 29, 2020.

Address for reprints: Sushrut S. Waikar, MD, MPH, Boston University Medical Center, Evans Biomedical Research Center, 5th Floor, 650 Albany St, Boston, MA 02118 (E-mail: swaikar@bu.edu).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2020.05.033

Abbreviations and Acronyms

AKI = acute kidney injury
CI = confidence interval
eGFR = estimated glomerular filtration rate
EPP = extrapleural pneumonectomy
HIOC = hyperthermic intraoperative chemotherapy
IQR = interquartile range
KDIGO = Kidney Disease Improving Global Outcomes
MPM = malignant pleural mesothelioma
P/D = pleurectomy/decortication
RRT = renal replacement therapy
SCr = serum creatinine

recurrence after treatment is common, highlighting the need for more aggressive local measures to eradicate microscopic tumor deposits. At our institution, we have previously demonstrated in several early-phase prospective trials the feasibility and safety of hyperthermic intraoperative chemotherapy (HIOC) involving cisplatin with or without gemcitabine, with reports of survival up to 35 months.[4,5] Intraoperative administration of high-dose chemotherapy to the pleural and peritoneal cavities after surgical resection is performed to enhance drug delivery and eliminate residual microscopic disease after macroscopic resection, while attempting to minimize systemic absorption. Hyperthermia increases the penetration of chemotherapy at the pleural and peritoneal surfaces and enhances cytotoxicity to tumor cells.[6,7] Despite its survival benefits, patients are at risk for a number of potential complications after surgery with HIOC, including acute kidney injury (AKI) and chronic kidney disease.[8]

AKI is common in the postoperative setting and has been demonstrated to occur in up to 30% of patients receiving high-dose intravenous cisplatin therapy.[9] AKI is associated with increased mortality, higher medical costs, longer length of stay, and higher risk of developing chronic kidney disease and cardiovascular disease.[10,11] Postoperative AKI has been studied most extensively in the settings of cardiac surgery, after which even small increases in postoperative serum creatinine (SCr) concentrations portend an increased risk of death.[12] AKI after surgery is attributed to ischemic injury, cytokine release, hemolysis, and oxidative stress, all of which can cause tubular injury, a major pathological correlate of ischemic AKI.[13] Tubular injury is also the hallmark of cisplatin nephrotoxicity, which is often used in animal models of AKI and is thought to occur as the result of direct cytotoxicity.[14-16] The combination of ischemic injury with nephrotoxic injury from HIOC would be expected to result in high rates of AKI, but has not been well studied. In this study, we sought to characterize the risk and outcomes of AKI after surgical resection of MPM with or without HIOC. We hypothesized that AKI would be more common in those treated with HIOC and that AKI would be associated with a higher risk of adverse events, including longer length of stay and increased mortality.

MATERIALS AND METHODS

We studied patients who had undergone surgical resection for MPM at Brigham and Women's Hospital between 2006 and 2015. Prospective informed consent was obtained from all patients for a study involving urine sample collection for biomarker evaluations for AKI. Data were obtained electronically from the Research Patient Data Registry and by review of progress notes. The prospective biosample collection study and the retrospective data analysis were both approved by the Partners Health Care Human Research Committee. Inclusion criteria for surgical therapy or intraoperative chemotherapy included the following: age 18 years or more, Karnofsky performance status greater than 70, normal liver function (aspartate aminotransferase < 80 IU/L, total bilirubin < 1.9 mg/dL, prothrombin time < 15 seconds), SCr less than 1.5 mg/dL, estimated glomerular filtration rate (eGFR) greater than 45 mL/min, partial pressure of carbon dioxide less than 45 mm Hg at room air, partial pressure of oxygen greater than 65 mm Hg at room air, predicted postoperative forced expiratory volume in 1 second greater than 0.8 L by pulmonary function tests and quantitative ventilation-perfusion scans, and grossly normal cardiac function by electrocardiography and echocardiography (left ventricular ejection fraction > 45%).

Patients underwent extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D) with or without HIOC. EPP consisted of en bloc resection of the lung, pleura, ipsilateral diaphragm, and pericardium, followed by reconstruction of the diaphragm and pericardium with a prosthetic patch made of Gore-Tex (WL Gore and Associates, Flagstaff, Ariz).[17] The choice of EPP or P/D was based on preoperative or intraoperative assignment by the surgeon as appropriate to the patient's disease burden, physiologic fitness, and potential for macroscopic complete resection. The use of HIOC versus no HIOC was based on enrollment in phase I/II trials or off-study based on prior established safety parameters and cisplatin maximal tolerated doses.[4,5] Patients were admitted the night before surgery and hydrated with 150 mL/h of normal saline. After resection of the entire specimen, patients treated with HIOC received intraoperative intracavitary lavage with a solution of 175 to 225 mg/m^2 cisplatin and/or 900 mg/m^2 gemcitabine in dialysate (Baxter, Deerfield, Ill) maintained at 42°C, as previously described.[5,18] Intravenous sodium thiosulfate was administered intraoperatively to promote binding of the absorbed cisplatin (4 g/m^2 followed by a 12 g/m^2 infusion), and patients were given liberal fluid replacement intraoperatively to maintain intravascular volume. Amifostine, a cytoprotective agent used to prevent nephrotoxicity,[13] was also administered intravenously to patients who received cisplatin at a dose of 910 mg/m^2 before intrathoracic cisplatin and 500 mg/m^2 2 hours later. All patients had a thoracic epidural catheter placed for pain control, with all surgical procedures performed under general anesthesia.

We defined baseline SCr as the value measured the day before surgery, before hydration with intravenous normal saline overnight. If no SCr value was available from the day before surgery, we designated the SCr value on the morning of the surgery as the baseline. Preoperative GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.[19] Using SCr values from the entire hospital stay, we defined AKI using the Kidney Disease Improving Global Outcomes (KDIGO) definition: an increase in SCr of 0.3 mg/dL or greater within 48 hours of surgery or a 50% or greater increase over 7 days.[20] We defined stages of AKI using the KDIGO definitions based on SCr increases: stage 1, 0.3 mg/dL or greater within 48 hours or 50% to 99% increase over baseline; stage 2, 100% to 199% increase over baseline; stage 3, 200% or greater over baseline or increase in SCr to 4.0 mg/L or greater or initiation of renal

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replacement therapy (RRT). We reviewed billing codes and progress notes to ascertain requirements for RRT (continuous venovenous hemofiltration or hemodialysis) during the index hospitalization. We reviewed progress notes and telephone encounters from the electronic medical record along with data from the Social Security Death Index for vital status.

Statistical Analysis

Descriptive statistics were summarized and presented as frequencies, mean ± standard deviation, or median with interquartile range (IQR). We assessed all variables for normality and log-transformed as appropriate. We compared continuous variables with Kruskal–Wallis test or analysis of variance as appropriate, and categoric variables with chi-square tests (Fisher exact if $n < 5$ in cells). Predictors for incident AKI (Y/N) were selected on the basis of clinical and biological relevance. To identify significant risk factors for AKI from among these candidate predictors, we considered several automated selection procedures such as stepwise, backward elimination, forward selection, and best subset regression. Because all results were similar, we present results from a stepwise forward selection algorithm (with $P \leq .05$ for entry and stay criteria). Complete data were available for all covariates except for estimated blood loss, which was missing in 14.3% and for which multivariate normal imputation was used for univariate logistic regression models using PROC MI in SAS (SAS Institute Inc, Cary, NC). We assessed differences in the rate of death on the basis of the occurrence and severity of AKI using Kaplan–Meier curves and the log-rank test, followed by multivariable-adjusted Cox proportional hazards models adjusted for age, sex, serum albumin, hypertension, diabetes, type and duration of surgery, and use of cisplatin before or during surgery.

We confirmed no violations of the proportional hazards assumption using the Kolmogorov-type supremum test, and the functional forms of the covariates were assessed by checking martingale residuals. Statistical tests were 2-tailed. All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc).

RESULTS

Study Population Characteristics

The cohort consisted of 503 patients with a mean age of 67.1 ± 10.1 years and baseline eGFR of 85.5 ± 24.8 mL/min/1.73 m^2. The majority were male and white. The surgical procedures were EPP in 241 patients (47.9%) and P/D in 262 patients (52.1%). Cisplatin HIOC was administered in 412 individuals (81.9%) as a single agent (n = 170) or with gemcitabine (n = 242).

Occurrence of Acute Kidney Injury

AKI developed in approximately half of the patients, the majority of which was KDIGO stage 1. RRT during the index hospitalization was required in 16 patients (3.2%). Table 1 shows clinical characteristics according to the presence or absence of AKI and its severity. AKI was more common in men than in women (54.6% vs 28.0%, $P < .001$), in patients who underwent EPP compared with pleurectomy (53.9% vs 43.1%, $P = .02$), and in those who received intraoperative cisplatin with or without gemcitabine compared with no cisplatin (53.6% vs 24.2%, $P < .001$). There was no significant difference in AKI between subjects who received cisplatin as a single agent intraoperatively versus those who received cisplatin with gemcitabine (54.7% vs 52.9%, $P = .72$). AKI was most frequently nonoliguric (Table 2); the median urine output of the 16 patients who required RRT was 1520 mL/24 hours (range, 203-6495 mL/24 hours) on the day of RRT initiation. All patients who required RRT had received intraoperative cisplatin. Patients who developed AKI had greater estimated blood loss in the operating room (median 1500 vs 1200 mL, $P < .001$) and longer surgery time (median 7.6 vs 7.1 hours, $P < .001$). From the stepwise multivariable logistic regression models, significant predictors for incident AKI included male sex, intraoperative cisplatin administration, prior cisplatin exposure, hypertension, higher baseline eGFR, and longer total surgery time (Table 3). A Hosmer–Lemeshow test for the multivariable model was not significant ($P = .67$) indicating good model calibration.

Outcomes After Acute Kidney Injury

The median length of stay was 13 days (IQR, 10-17) in those without AKI compared with 14 days (IQR, 10-20), 15 days (IQR, 11-22.0), and 26 days (IQR, 17-45) in those with AKI stage 1, 2, and 3, respectively. A total of 347 patients (68.9%) died after a total follow-up time of 908 person-years. The death rate (per 100 person-years) was 32.9, 41.4, 51.6, and 106 in those without AKI and with AKI stages 1, 2, and 3, respectively. Figure 1 shows Kaplan–Meier curves for time to death according to the presence and severity of AKI. AKI stages 1, 2, and 3 were associated with a 1.15 (95% confidence interval [CI], 0.90-1.47), 1.25 (95% CI, 0.79-1.98), and 2.71-fold (95% CI, 1.65-4.45) increased risk of death in multivariable-adjusted models, respectively. Although this study was not designed to study treatment effects, we found that the use of HIOC with cisplatin was associated with a greater risk of AKI but a lower risk of death (Table 4). Figure 2 describes the main results of the study.

DISCUSSION

In this retrospective review of a prospectively assembled cohort study of patients undergoing cytoreductive surgery with or without HIOC for MPM, we found evidence in support of our hypothesis that AKI would be common with HIOC and associated with adverse events. Our results showed that approximately half of patients developed postoperative AKI, and 3.2% required RRT. The risk of AKI in this cohort exceeds the risk reported in other postoperative settings such as cardiac surgery and is noteworthy considering that the baseline level of kidney function was relatively normal (preexisting chronic kidney disease is a relative contraindication to cytoreductive surgery). By comparison, the risk of postoperative AKI requiring RRT after cardiac surgery is approximately 1% and is almost exclusively seen in those with preexisting CKD.[21] Male sex, previous exposure to cisplatin, and intraoperative cisplatin administration were independently associated with a higher

TABLE 1. Demographic and clinical characteristics of patients according to the development of acute kidney injury

	No AKI (n = 260)	Any AKI (n = 243)	*P* value*	AKI stage 1 (n = 189)	AKI stage 2 (n = 32)	AKI stage 3 (n = 22)
Demographics						
Mean age, y	66.9 ± 10.6	67.3 ± 9.5	.63	67.4 ± 9.7	69.6 ± 7.4	63.1 ± 9.5
Male sex No. (%)	175 (67.3)	210 (86.4)	<.001	164 (86.8)	28 (87.5)	18 (81.8)
White race No. (%)	255 (98.1)	236 (97.1)	.68	184 (97.4)	32 (100.0)	20 (90.9)
Medical history No. (%)						
Diabetes mellitus	43 (16.5)	32 (13.2)	.35	20 (10.6)	8 (25.0)	4 (18.2)
Hypertension	125 (48.1)	139 (57.2)	.05	109 (57.7)	21 (65.6)	9 (40.9)
Coronary artery disease	34 (13.1)	31 (12.8)	.99	27 (14.3)	4 (12.5)	0 (0.0)
Prior cisplatin exposure	46 (17.7)	49 (20.2)	.55	37 (19.6)	7 (21.9)	5 (22.7)
Prior asbestos exposure	170 (65.4)	169 (69.5)	.39	131 (69.3)	26 (81.2)	12 (54.5)
Current/prior smoking	146 (49.6)	146 (60.0)	.57	114 (60.3)	22 (68.8)	10 (45.5)
Baseline renal function						
Mean SCr, μmol/L	80.4 ± 24.8	78.7 ± 20.3	.32	80.4 ± 21.2	73.4 ± 21.2	74.3 ± 16.8
Mean eGFR, mL/min/1.73 m^2	82.2 ± 22.7	89.1 ± 26.6	.002	87.7 ± 26.9	95.0 ± 27.1	92.4 ± 22.0
Medications No. (%)						
RAAS inhibitors	74 (28.5)	74 (30.5)	.70	57 (30.2)	13 (40.6)	4 (18.2)
Beta-blockers	73 (28.1)	70 (28.8)	.93	58 (30.7)	7 (21.9)	5 (22.7)
Calcium channel blockers	31 (11.9)	35 (14.4)	.49	27 (14.3)	7 (21.9)	1 (4.5)
Diuretics	49 (18.8)	42 (17.3)	.74	34 (18.0)	5 (15.6)	3 (13.6)
Statins	96 (36.9)	90 (37.0)	1.0	69 (36.5)	14 (43.8)	7 (31.8)
Proton pump inhibitors	57 (21.9)	34 (14.0)	.03	29 (15.3)	4 (12.5)	1 (4.5)
NSAIDs	27 (10.4)	30 (12.3)	.58	24 (12.7)	4 (12.5)	2 (9.1)
Surgery details						
EPP No. (%)	111 (42.7)	130 (53.5)		97 (51.3)	13 (40.6)	20 (90.9)
Pleurectomy No. (%)	37 (14.2)	21 (8.6)	<.001	16 (8.5)	4 (12.5)	1 (4.5)
Radical pleurectomy No. (%)	112 (43.1)	92 (37.9)		76 (40.2)	15 (46.9)	1 (4.5)
Mean length of surgery, h	7.1 (2.0)	7.8 (1.6)	<.001	7.8 (1.6)	7.7 (1.4)	7.4 (1.5)
Mean estimated blood loss, mL	1472 (1022)	1697 (1202)	.04	1694 (1277)	1765 (977)	1621 (740)
Intraoperative chemotherapy						
None	60 (23.1)	19 (7.8)		14 (7.4)	4 (12.5)	1 (4.5)
Cisplatin only	77 (29.6)	93 (38.3)	<.001	72 (38.1)	11 (34.4)	10 (45.5)
Gemcitabine only	9 (3.5)	3 (1.2)		3 (1.6)	0 (0.0)	0 (0.0)
Cisplatin and gemcitabine	114 (43.8)	128 (52.7)		100 (52.9)	17 (53.1)	11 (50.0)

AKI, Acute kidney injury; *SCr*, serum creatinine; *eGFR*, estimated glomerular filtration rate; *RAAS*, renin angiotensin aldosterone system; *NSAID*, nonsteroidal anti-inflammatory drug; *EPP*, extrapleural pneumonectomy. *Comparing no AKI with any AKI.

risk of AKI. Patients who developed severe AKI had a longer length of hospital stay and higher risk of death.

AKI rates are highly variable among patients undergoing cytoreductive surgery without HIOC. EPP is a more extensive surgery than P/D, involving en bloc resection of the lung, ipsilateral diaphragm, pericardium, and parietal pleura, and is therefore associated with a high rate of postoperative complications. In a study from our institution on adverse events associated with EPP without HIOC, Sugarbaker and colleagues[18] reported that 9 of 328 patients (2.7%) developed postoperative AKI, defined as the need for RRT. Patients with a baseline SCr less than 2 mg/dL were deemed ineligible for EPP. AKI was thought to result in the death of 1 patient and was associated with acute respiratory distress syndrome and multiple organ dysfunction. Other studies of postoperative morbidity and mortality after neoadjuvant chemotherapy and EPP have not reported significant renal complications, which suggests that HIOC with cisplatin may play a role in the increased risk of AKI in this population.[22,23]

HIOC is now commonly used after surgical resection with EPP or P/D to improve locoregional control at sites with potential microscopic disease and reduce the risk of recurrence.[4] The technique has been used in the setting of a number of malignancies with pleural and peritoneal involvement, including peritoneal mesothelioma,[24] thymoma,[25] and ovarian cancer.[26] Despite its associated survival benefits, we found that the risk of AKI was higher among patients receiving high-dose cisplatin HIOC. Although most of the events were mild (KDIGO stage 1

TABLE 2. Urine output at the time of severe acute kidney injury

	Time to AKI stage 3 (days after surgery)	Urine output at time of AKI stage 3 (mL/24 h)	Time to RRT initiation (days after surgery)	Urine output at time of RRT initiation (mL/24 h)
Patient 1	-	-	16	3575
Patient 2	-	-	20	6495
Patient 3	3	1335	-	-
Patient 4	3	4755	9	1035
Patient 5	2	3855	5	1155
Patient 6	5	7160	-	-
Patient 7	2	Nonoliguric*	9	1830
Patient 8	2	4000	8	562
Patient 9	2	3255	13	203
Patient 10	3	3920	9	2424
Patient 11	3	815	11	1550
Patient 12	5	1805	-	-
Patient 13	2	6310	6	978
Patient 14	4	2278	-	-
Patient 15	2	2000	8	1450
Patient 16	4	2160	-	-
Patient 17	17	1310	21	1520
Patient 18	-	-	14	2690
Patient 19	3	1673	5	3000†
Patient 20	3	Nonoliguric*	-	-
Patient 21	20	Oliguric*	35	2440
Patient 22	12	Nonoliguric*	16	1450

AKI, Acute kidney injury; *RRT*, renal replacement therapy. *Exact urine output not reported in the medical chart. †Approximate urine output extrapolated from chart report of 20 to 30 mL/h.

AKI), severe AKI requiring RRT was observed in 3.2% of patients. These findings have been observed in other studies. A single-center study comparing cytoreductive surgery with or without hyperthermic intraperitoneal cisplatin found that AKI occurred in 10 of 32 (31.2%) versus 4 of 34 (11.7%) in those who did versus not receive hyperthermic intraperitoneal cisplatin.[27] In a phase 1 clinical trial designed to establish the maximum tolerated dose of HIOC after EPP or P/D, 3 of 19 patients receiving high-dose cisplatin (225 mg/m^2) and gemcitabine therapy developed grade 4 AKI (life-threatening, requiring RRT).[5] The frequency of severe AKI prompted protocol review and reduction in the dose of cisplatin to 175 mg/m^2. Although there were fewer severe AKI events among patients treated with the lower dose of cisplatin in combination with 1000 to 1200 mg/m^2 of gemcitabine (n = 29), there were still 2 reported cases of grade 1 (mild) and 1 case of grade 4 AKI. The observed rates of AKI are not just isolated to patients with MPM. In a multicenter, phase 3 trial of HIOC in stage III epithelial cancer, 245 patients were randomized to cytoreductive surgery with or without the addition of HIOC with cisplatin.[26] Among those patients undergoing surgery alone, 3 experienced AKI (2%), compared with 5 patients (4%) in the surgery with HIOC.

AKI and its association with higher mortality can be attributed to factors intrinsic to the surgery itself, as well as to the direct toxic effects of cisplatin. AKI is common after major surgery and has been associated with increased length of stay and higher mortality.[28,29] We found that stage 3 AKI portended a greater risk of death. The majority of patients requiring RRT (all of whom received cisplatin) had preserved urine output, which is common with cisplatin nephrotoxicity.[30] Despite intrathoracic administration of cisplatin, there is systemic absorption of the heated solution lavaged through the thoracic cavity; the proximal tubules, which are already at risk of injury from factors related to major surgery, are therefore exposed to the cytotoxic effects of cisplatin. The extent of cisplatin absorption into the circulation during HIOC has been studied previously,[31] with one report suggesting that one-third of the intrathoracic administered dose reaches the systemic circulation within 90 minutes of perfusion[32] and another reporting comparable

TABLE 3. Risk factors for acute kidney injury, defined as an increase in serum creatinine of at least 0.3 mg/dL within 48 hours or surgery or greater than 50% increase in serum creatinine over 7 days

	Univariate logistic regression		Stepwise logistic regression	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.00 (0.98-1.01)	.63	-	-
Male (vs female)	3.09 (1.97-4.84)	<.0001	2.98 (1.85-4.80)	<.0001
Diabetes mellitus (vs no)	0.76 (0.47-1.25)	.29	-	-
Previous cisplatin exposure (vs no)	1.17 (0.75-1.84)	.48	1.96 (1.17-3.27)	.02
Hypertension (vs no)	1.44 (1.02-2.05)	.04	1.57 (1.06-2.32)	.02
Coronary artery disease (vs no)	0.97 (0.57-1.63)	.91	-	-
Baseline eGFR (per 10 mL/min/1.73 m^2)	1.01 (1.00-1.02)	.002	1.01 (1.00-1.02)	.032
Current smoker (vs no)	1.21 (0.83-1.75)	.36	-	-
Prior smoker (vs no)	1.01 (0.56-1.82)	.77	-	-
EPP (vs other)	1.55 (1.08-2.19)	.02	-	-
Intraoperative cisplatin (vs no)	3.62 (2.16-6.09)	<.0001	3.12 (1.77-5.5)	<.0001
Total surgical time (per hour)	1.25 (1.12-1.39)	<.0001	1.15 (1.02-1.28)	.02
Estimated blood loss (per L)	0.85 (0.71-1.02)	.08	-	-
Albumin (per g/dL)	0.84 (0.56-1.26)	.40	-	-
Statins (vs no)	1.01 (0.70-1.44)	.98	-	-
NSAIDs (vs no)	1.21 (0.70-2.11)	.49	-	-
Beta-blockers (vs no)	1.04 (0.70-1.52)	.85	-	-
PPIs (vs no)	1.73 (1.08-2.75)	.02	-	-
RAAS inhibitors (vs no)	1.01 (0.75-1.61)	.62	-	-
Calcium channel blockers (vs no)	1.24 (0.74-2.09)	.41	-	-

OR, Odds ratio; *CI*, confidence interval; *eGFR*, estimated glomerular filtration rate; *EPP*, extrapleural pneumonectomy; *NSAID*, nonsteroidal anti-inflammatory drug; *PPI*, proton pump inhibitor; *RAAS*, renin angiotensin aldosterone system.

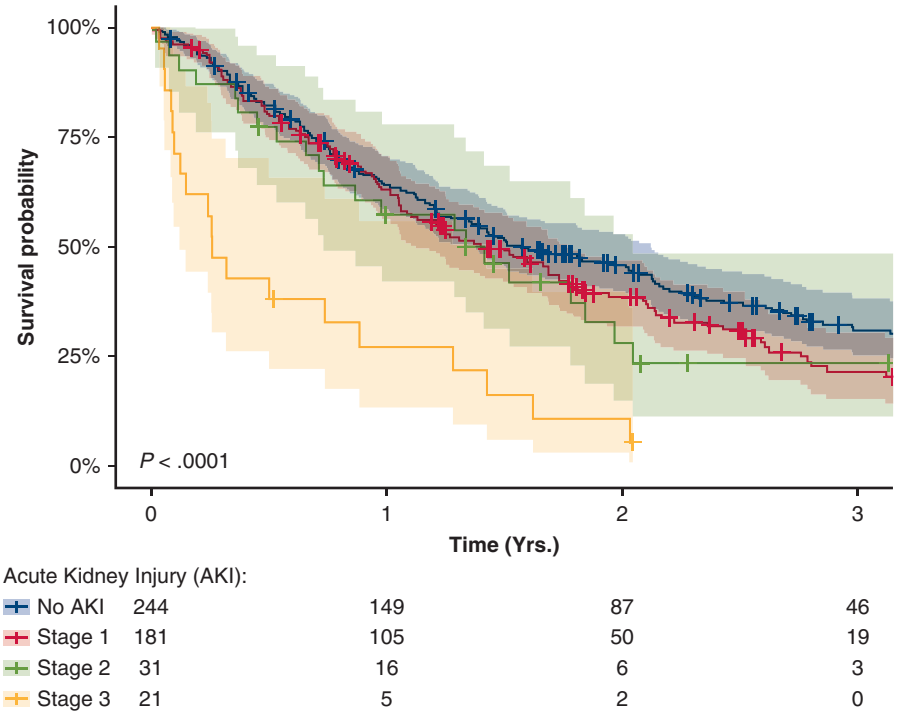

FIGURE 1. Long-term mortality after cytoreductive surgery with or without heated intraoperative chemotherapy with cisplatin, based on the occurrence and severity of AKI. AKI was defined as an increase in SCr of 0.3 mg/dL or greater within 48 hours of surgery or a 50% or greater increase over 7 days. Stages of AKI were defined as stage 1, 0.3 mg/dL or greater within 48 hours or 50% to 99% increase over baseline; stage 2, 100% to 199% increase over baseline; stage 3, 200% or greater over baseline or increase in SCr to 4.0 mg/L or greater or initiation of RRT.

TABLE 4. Outcomes in those who did versus did not receive hyperthermic intraoperative chemotherapy with cisplatin

	HIOC with cisplatin	
	No	Yes
N	91	412
Risk of AKI	22 (24.2%)	221 (53.6%)
Median LOS	14 d (IQR, 10-21)	13.5 d (IQR, 10-20)
Risk of death	73 (80.2%)	274 (66.5%)

HIOC, Hyperthermic intraoperative chemotherapy; *AKI*, acute kidney injury; *LOS*, length of stay; *IQR*, interquartile range.

levels in plasma after HIOC compared with intravenous administration of a similar dose of cisplatin.[33]

We identified certain clinical and demographic characteristics that were associated with a higher risk of AKI. For instance, men were at substantially higher risk of postoperative AKI than women. The literature on sex differences in AKI risk is variable. In 2 meta-analysis studies reporting sex-stratified data on the incidence of AKI in hospitalized individuals, men were reported to have 1.23-fold higher odds of AKI and 2.19-fold higher odds of AKI requiring dialysis than women.[34,35] In experimental models of ischemia–reperfusion injury, male rodents are more susceptible to kidney injury than female rodents, possibly from testosterone's effect on reducing ischemia-induced activation of nitric oxide synthases.[36] Similar sex-related differences in susceptibility to cisplatin toxicity have also been reported in other animal models.[37] In addition to male versus female sex, we found that previous exposure to cisplatin was associated with a higher risk of AKI. This may reflect prior subclinical tubular injury from cisplatin toxicity, rendering the proximal tubule vulnerable to further damage. Our finding that higher eGFR was associated with a higher risk of AKI was surprising and is likely due to confounding from muscle mass, with lower muscle mass and cachexia leading to lower SCr (and higher eGFR) for any given level of kidney function.[38]

Study Limitations

Our study evaluates the incidence of AKI at one of the pioneer centers for multimodality therapy for MPM. There

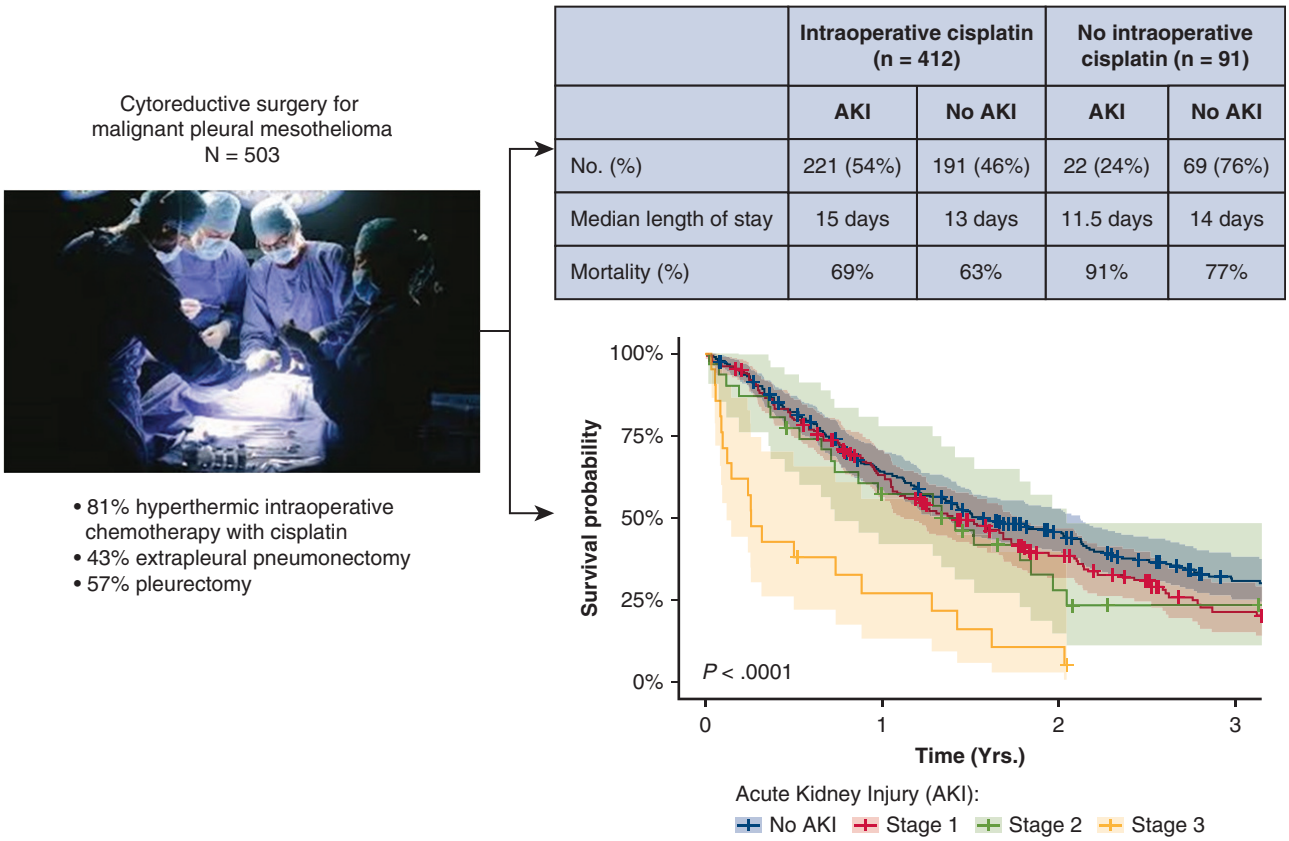

FIGURE 2. We examined the risk of AKI in patients undergoing cytoreductive surgery for MPM with or without intraoperative chemotherapy with cisplatin. Overall, 48% of patients developed AKI, defined as an increase in SCr of 0.3 mg/dL or greater within 48 hours of surgery or a 50% or greater increase over 7 days. Stages of AKI were defined as stage 1, 0.3 mg/dL or greater within 48 hours or 50% to 99% increase over baseline; stage 2, 100% to 199% increase over baseline; stage 3, 200% or greater over baseline or increase in SCr to 4.0 mg/L or greater or initiation of RRT. Compared with those who did not develop AKI, those with stage 3 AKI had a 2.71-fold increased risk of death.

are several limitations to our study to consider. Generalizability is limited because this report is from a single center that performs a technically demanding and complex surgical procedure with intraoperative chemotherapy in a patient population with a rare malignancy and limited life expectancy. Nevertheless, the frequency and nature of AKI, which likely occurred from a combination of ischemic and/or nephrotoxic injury, may help inform risk prediction in other types of AKI. The data used in this study were not collected specifically for investigating risk factors for AKI or for comparing survival differences across treatment strategies; therefore, information on variables such as intraoperative hypotension, vasopressor requirement, and diuretic administration, and oncology-specific data were not available. The protocol at our institution includes both prophylactic thiosulfate and amifostine administration as the standard of care in all patients receiving intrathoracic cisplatin. We were accordingly unable to compare the association between prophylactic thiosulfate or amifostine and the development of AKI. Nevertheless, our finding of an association between the severity of AKI and adverse outcomes, including longer length of stay and increased postoperative mortality, highlights the importance of AKI prevention when using multimodality therapies to treat MPM. Our finding that a survival benefit with HIOC with cisplatin was limited to those who did not develop AKI also underscores the importance of prevention strategies to reduce the risk of AKI. Other strategies for AKI prevention should be tested in this high-risk patient population.

CONCLUSIONS

Our study highlights risk factors, incidence, and outcomes of AKI after cytoreductive surgery with or without HIOC for MPM. Given the highly aggressive nature and poor prognosis of MPM, along with the potential of multimodality therapies to extend overall survival, strategies geared toward prevention and early recognition of AKI would have important implications for the care of these complex patients.

Conflict of Interest Statement

S.S. Waikar reports consulting fees from Public Health Advocacy Institute, CVS, Roth Capital Partners, Kantum, Mallinckrodt, Wolters Kluewer, GE Health Care, GSK, Mass Medical International, JNJ, Venbio, Strataca, Takeda, Cerus, Pfizer, and Allena. D.E. Leaf reports research funding from BioPorto Diagnostics. G. Frendl reports funding from Merck for a clinical trial unrelated to this project. S.M. reports salary from Wolters Kluwer (UpToDate) as Deputy Editor. R. Bueno reports a financial relationship with the National Cancer Institute, Department of Defense, Siemens, Roche-Genentech, Verastem, Gritstone, Merck, Medgenome, and Navigation Sciences. S. Gupta reports research funding from the National Institutes of Health and National Institute on Deafness and Other Communication Disorders, as well as personal fees: Scientific coordinator for GlaxoSmithKline's ASCEND trial. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: acute kidney injury, heated intrathoracic chemotherapy, malignant pleural mesothelioma, pleurectomy, pneumonectomy