OBSERVATIONAL STUDY

OPEN

Association of Preoperative Immune Checkpoint Inhibitor Therapy With Cardiopulmonary Instability and Organ Injury After High-Risk Surgery

Ying-Hung Tang, MD, MPH[1,2]

Jules Bergmann, MS, MD[3]

Dhananjay Vaidya, MBBS, PhD, MPH[4]

Nauder Faraday, MD, MPH[2,3]

OBJECTIVES: To assess the relationship between prior exposure to immune checkpoint inhibitors (ICIs) and the risk of postoperative complications in cancer patients.

DESIGN: Single-center retrospective cohort study

INTERVENTIONS: The main exposure was treatment with an FDA-approved ICI within 6 months before surgery.

MEASUREMENTS AND MAIN RESULTS: Exposure to ICIs and covariates was determined from the electronic health record. The primary outcome was a composite of postoperative complications, including prolonged pressor or oxygen dependence, kidney injury, or myocardial injury. Secondary outcomes included each subcomponent of the primary outcome. Of 7674 subjects with cancer admitted to the ICU after surgery, 247 were exposed to one or more ICIs in the 6 months before surgery. After propensity score matching, 197 ICI-exposed subjects were matched to 777 nonexposed. The composite outcome occurred in 70 of 197 (35.5%) ICI-exposed subjects and 251 of 777 (32.3%) nonexposed. There was no difference between exposed and nonexposed groups in the primary composite outcome (odds ratio [OR], 1.12; 95% CI, 0.80–1.58) by conditional logistic regression. Risk of the secondary outcome of prolonged pressor dependence was significantly higher in ICI-exposed subjects (OR, 1.64; 95% CI, 1.01–2.67). Risks of oxygen dependence (OR, 1.13; 95% CI, 0.75–1.73), kidney injury (OR, 1.15; 95% CI, 0.77–1.71), and myocardial injury (OR, 1.76; 95% CI, 1.00–3.10) were not significantly different. There was no difference between groups in the time to hospital discharge alive ($p = 0.62$).

CONCLUSIONS: Exposure to ICIs within 6 months before high-risk surgery was not associated with the composite outcome of cardiopulmonary instability or organ injury in patients with cancer. The potential for an association with the secondary outcomes of cardiac instability and injury is worthy of future study.

KEYWORDS: acute kidney injury; immune checkpoint inhibitors; myocardial injury; postoperative period; surgical complications

Immune checkpoint inhibitors (ICIs) have become a promising class of anti-cancer therapy with rapidly expanding indications including, but not limited to, melanoma, lung cancer, renal cancer, urothelial cell cancer, head-and-neck cancer, and microsatellite instability-high or mismatch repair deficient gastrointestinal malignancies (1). Two recent randomized controlled trials of neoadjuvant therapy for lung cancer with programmed cell death protein 1 (PD-1) inhibitors demonstrated improved 2-year survival and pathologic response (2, 3). Currently, Food and Drug Administration (FDA)-approved ICIs include PD-1 inhibitors (nivolumab, pembrolizumab,

DOI: 10.1097/CCE.0000000000001068

KEY POINTS

Question: Immune checkpoint inhibitors (ICIs) are associated with a wide range of systemic and organ-specific injuries. Is exposure to ICIs before surgery associated with higher risk of a composite outcome of cardiopulmonary instability and organ injury in patients with cancer?

Findings: ICI exposure in the 6 months before surgery was not significantly associated with a composite outcome of prolonged pressor or oxygen dependence, kidney injury, or myocardial injury after surgery. An association with the secondary outcome of prolonged pressor dependence was observed.

Meaning: Preoperative treatment of cancer patients with ICIs is not associated with a major increase in risk of a composite outcome of cardiac, pulmonary, and kidney complications; however, an association specific to cardiac complications cannot be excluded.

cemiplimab), programmed cell death ligand 1 (PD-L1) inhibitors (atezolizumab, avelumab, durvalumab), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors (ipilimumab), and lymphocyte activation gene 3 (LAG-3) inhibitors (relatlimab) (1, 4). These ICIs promote T-cell activation by blocking anergic signaling pathways and can impede tumor progression (5). In some patients, ICIs have been reported to trigger a spectrum of immune-related adverse events (irAEs), including nonspecific systemic inflammation (e.g., cytokine-release syndrome) and organ-specific inflammatory effects, such as nephritis, pneumonitis, and myocarditis (6, 7). Immune dysregulation and chronic irAEs (≥ 12 wk after ICI therapy) are reported to occur with some regularity, and these irAEs may persist for a year or more after ICI therapy (8). Despite immunologic risks, ICIs have gained an increasing role for earlier stage cancer amenable for surgical resection in the neoadjuvant setting because of their long-term benefits (1–3, 9).

The frequency of irAEs in surgical patients treated with ICIs is unclear. Previous studies have reported irAEs occurring in patients who underwent surgical resection for metastatic disease (10–13), as well as surgical patients who had received ICI therapy in the neoadjuvant setting (14–17). Given that surgical stress triggers an inflammatory response, prior exposure to ICIs might be associated with a higher frequency of systemic or organ-specific inflammatory complications after surgery. However, the relative frequency of postoperative complications in ICI exposed vs. ICI nonexposed patients has not been reported. In this retrospective cohort study, we examined a broad range of postoperative adverse events that could be triggered by immune activation and systemic inflammation, including prolonged pressor and oxygen dependence, as well as injuries specific to the kidney and heart. We hypothesized that cancer patients exposed to ICIs within 6 months before surgery would experience higher risk for postoperative cardiopulmonary instability and organ injury than nonexposed patients.

METHODS

Study Design and Data Collection

This retrospective cohort study included patients who underwent surgery at the Johns Hopkins Hospital (Baltimore, MD) from July 1, 2016, to June 30, 2021, and were at high risk for postoperative cardiopulmonary instability. All data elements were extracted from the electronic health record. Surgical cases were eligible for inclusion if the subject met the following criteria: 1) older than 18 years old and 2) admitted to ICU within 24 hours of the end of surgery. Surgical cases were excluded for the following: 1) subject did not have a diagnosis of cancer before surgery; 2) the procedure occurred in a non-operating room setting, for example, interventional radiology, endoscopy, etc.; 3) the surgical case was not the index procedure for a unique subject; or 4) missing data for a critical variable (i.e., ASA classification; **Fig. 1**).

Ethics Approval and Consent to Participant

Ethical review was performed by the Johns Hopkins Institutional Review Board, with reference number IRB00271579 and title "Derivation of novel features from time series physiologic data to identify and predict risk of adverse outcomes in high-risk surgical patients." The protocol was approved with waiver of informed consent on June 2, 2021.

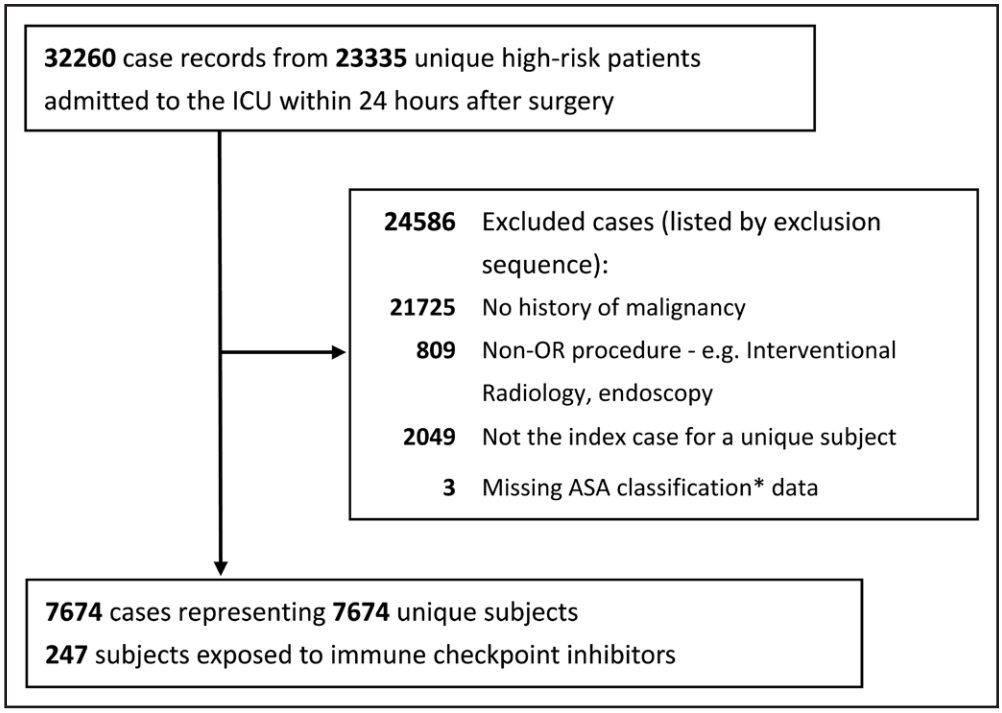

Figure 1. Patient eligibility flowchart. *American Society of Anesthesiologists physical status classification.

The study was conducted in compliance with the Declaration of Helsinki.

Exposure

The main exposure was treatment with any ICI within 180 days before the start of surgery. Types of ICIs identified in our study included PD-1 inhibitors, PD-L1 inhibitors, LAG-3 inhibitors, and CTLA-4 inhibitors. Patients exposed to any ICI were categorized as exposed.

Outcome Measures

The primary outcome was a composite of cardiopulmonary instability, kidney injury, or myocardial injury from the end of surgery to the time of hospital discharge. Cardiac instability was defined as the need for continuous IV infusion of a pressor (norepinephrine, phenylephrine, epinephrine, or dopamine) more than 24 hours after the end of surgery. Pulmonary instability was defined as the need for supplemental oxygen at greater than 40% more than 24 hours after the end of surgery. Kidney injury was defined in accordance with kidney disease improving global outcomes criteria as an increase in serum creatinine by 0.3 mg/dL within 48 hours after surgery or more than a 50% increase in creatinine within 7 days after surgery. Myocardial injury was defined as a troponin greater than 0.04 ng/mL (the 99th percentile for the assay) at any time after surgery and before hospital discharge. The primary outcome was defined as positive if the subject met criteria in one or more of the four subdomains (cardiac instability, pulmonary instability, kidney injury, or myocardial injury). Secondary outcomes included each subcomponent of the primary outcome and the time from end of surgery to discharge alive. (Cardiac surgery cases were excluded from the subdomain outcome of myocardial injury because of the challenge interpreting troponin values after cardiac surgery).

Covariates

Subject characteristics included demographic variables, baseline comorbidities, chemotherapeutic drug exposures, and operative variables (**Table 1**; and **Supplemental Table 1**, http://links.lww.com/CCX/B323, for full list of covariates). Baseline comorbidities were determined from *International Classification of Diseases*, 10th Edition codes available from the electronic health record. Comorbidities were categorized using methods described for the Elixhauser Comorbidity Index where appropriate (18). Exposure to common chemotherapeutic agents that are used to treat malignancies linked to ICIs (19) was also determined from the electronic health record. The following chemotherapy agents were grouped into subclasses (Table 1) and categorized as administered/not administered within the 180 days before surgery: Platinum-containing agents (cisplatin and carboplatin), nitrogen mustards (cyclophosphamide), taxanes (paclitaxel and docetaxel), topoisomerase antagonists (doxorubicin, epirubicin, irinotecan,

TABLE 1.
Baseline Preoperative Characteristics of the Study Sample Before and After Propensity Score Matching

Matched Covariates	Before Matching ($n = 7674$)			After Matching ($n = 974$)		
	Exposed ($n = 247$)	Nonexposed ($n = 7427$)	ASD	Exposed ($n = 197$)	Nonexposed ($n = 777$)	ASD
Age, mean (SD), yr	64.7 (11.4)	62.7 (14.4)	0.15	64.3 (12.0)	64.0 (13.9)	0.02
Female, *n* (%)	98 (39.7)	3328 (44.8)	0.10	75 (38.1)	291 (37.5)	0.01
Underlying malignancy, *n* (%)						
Pancreas	79 (32.0)	1138 (15.3)	0.40	30 (15.2)	128 (16.5)	0.03
Lung	40 (16.2)	548 (7.4)	0.28	40 (20.3)	144 (18.5)	0.04
Esophagus/stomach/intestine	31 (12.6)	1130 (15.2)	0.08	29 (14.7)	113 (14.5)	0.01
Urinary tract	30 (12.1)	589 (7.9)	0.14	29 (14.7)	109 (14.0)	0.02
Malignant melanoma	17 (6.9)	274 (3.7)	0.14	17 (8.6)	81 (10.4)	0.06
Other skin cancer	24 (9.7)	782 (10.5)	0.03	21 (10.7)	84 (10.8)	0.00
Liver/biliary	24 (9.7)	430 (5.8)	0.15	24 (12.2)	93 (12.0)	0.01
Breast	17 (6.9)	576 (7.8)	0.03	12 (6.1)	58 (7.5)	0.05
Other malignancy	26 (10.5)	2638 (35.5)	0.62	26 (13.2)	110 (14.2)	0.03
Exposure to chemotherapeutic agents within 180 d before surgery, *n* (%)						
Platinum-containing agents	32 (13.0)	213 (2.9)	0.38	32 (16.2)	92 (11.8)	0.13
Cyclophosphamide	62 (25.1)	55 (0.7)	0.78	12 (6.1)	42 (5.4)	0.03
Taxanes	25 (10.1)	205 (2.8)	0.30	25 (12.7)	73 (9.4)	0.11
Topoisomerase antagonists	22 (8.9)	293 (3.9)	0.20	14 (7.1)	48 (6.2)	0.04
Other	20 (8.1)	206 (2.8)	0.24	20 (10.2)	61 (7.9)	0.08
Comorbidities, *n* (%)						
Coronary artery disease	53 (21.5)	1792 (24.1)	0.06	46 (23.4)	197 (25.4)	0.05
Congestive heart failure	10 (4.0)	677 (9.1)	0.21	10 (5.1)	47 (6.0)	0.04
Valvular disease	10 (4.0)	494 (6.7)	0.12	6 (3.0)	29 (3.7)	0.04
Chronic pulmonary disease	36 (14.6)	1251 (16.8)	0.06	29 (14.7)	134 (17.2)	0.07
Pulmonary circulation disorder	5 (2.0)	98 (1.3)	0.05	5 (2.5)	16 (2.1)	0.03
Obstructive sleep apnea	26 (10.5)	1025 (13.8)	0.10	23 (11.7)	87 (11.2)	0.02
Liver disease	22 (8.9)	665 (9.0)	0.00	18 (9.1)	78 (10.0)	0.03
Peripheral vascular disease	6 (2.4)	491 (6.6)	0.20	6 (3.0)	28 (3.6)	0.03
Rheumatoid arthritis/collagen vascular disease	5 (2.0)	199 (2.7)	0.04	4 (2.0)	21 (2.7)	0.04
Coagulation deficiency	18 (7.3)	514 (6.9)	0.01	15 (7.6)	57 (7.3)	0.01
Diabetes mellitus	49 (19.8)	1650 (22.2)	0.06	38 (19.3)	149 (19.2)	0.00
Hypertension	124 (50.2)	3360 (45.2)	0.10	100 (50.8)	392 (50.5)	0.01
Renal failure	13 (5.3)	726 (9.8)	0.17	12 (6.1)	55 (7.1)	0.04
Obesity	32 (13.0)	1321 (17.8)	0.13	29 (14.7)	131 (16.9)	0.06
Weight loss	29 (11.7)	711 (9.6)	0.07	26 (13.2)	86 (11.1)	0.07

(*Continued*)

TABLE 1. (*Continued*)
Baseline Preoperative Characteristics of the Study Sample Before and After Propensity Score Matching

	Before Matching ($n = 7674$)			After Matching ($n = 974$)		
Matched Covariates	Exposed ($n = 247$)	Nonexposed ($n = 7427$)	ASD	Exposed ($n = 197$)	Nonexposed ($n = 777$)	ASD
Electrolyte disorder	15 (6.1)	931 (12.5)	0.22	13 (6.6)	52 (6.7)	0.00
Blood loss anemia	3 (1.2)	89 (1.2)	0.00	2 (1.0)	6 (0.8)	0.03
Deficiency anemia	34 (13.8)	1186 (16.0)	0.06	31 (15.7)	122 (15.7)	0.00

ASD = absolute standardized difference.

and etoposide), and other agents (methotrexate, pemetrexed, capecitabine, gemcitabine, vinorelbine, vinblastine, eribulin, bevacizumab, and trastuzumab). The type of surgical procedure was identified from the electronic health record and categorized by anatomical site as follows: abdominal/gastrointestinal, brain, urologic, thoracic, head and neck, musculoskeletal, cardiac, spine, and other. Additional covariates included ASA physical status, emergency status of the operation, duration of anesthesia, and time from the end of surgery to admission to the ICU.

Statistical Analysis

Each subject's propensity to receive ICI was estimated using a logistic regression model, with the matching covariates (listed in Table 1; and Supplemental Table 1, http://links.lww.com/CCX/B323) set as the independent variables. Subjects exposed to ICIs were each matched with up to four unexposed subjects using the logit of the propensity score through the approach of greedy matching algorithm without replacement. The caliper width was set at 0.2 of the logit of the SD of the propensity score (20). The matching process was carried out by the CALIPMATCH command package using STATA, Version 18.0 (StataCorp LLC, College Station, TX). Standardized mean differences of each matched covariate were calculated in absolute values for balance diagnostics between the matched groups, and a difference greater than 0.1 was considered imbalanced (21). Continuous variables are represented as mean ± SD and categorical variables as proportion (%).

For the primary outcome, we used conditional logistic regression models to calculate odds ratios (ORs) and 95% CIs in the propensity-matched cohort. Covariates with absolute standardized differences greater than 0.1 were included in the adjusted regression model. Conditional logistic regression with adjustment for imbalanced covariates was also used to calculate ORs for the secondary outcomes, which consisted of each of the four subdomains of the composite outcome. Exploratory analyses for heterogeneity in ORs for the primary outcome were planned a priori for subgroups by age, sex, cancer type, and surgical procedure. We also explored the association between the primary outcome and exposure to different types of ICIs. We used the Kaplan-Meier method for the secondary outcome of time to hospital discharge alive. Subjects were censored for death or at 30 days, whichever came first. The log-rank test was used to examine the difference between ICI-exposed and nonexposed groups.

We estimated the minimum detectable OR for the composite outcome in the exposed group based on a total of 1250 subjects in the study cohort with 4:1 matching of controls to cases. Previous studies in high-risk surgical cohorts reported adverse outcomes as follows: 10% pressor dependence (22), 3.4–23% lung injury (22–24), 12.0–22.7% acute kidney injury (25–27), and 11.6–14.1% myocardial injury (28, 29). Assuming the composite outcome occurred in 30% of controls, power of 0.8, and alpha of 0.05, we estimated a minimal detectable OR of 1.51 in the ICI group.

All analyses were performed using STATA, Version 18.0 (StataCorp LLC). Statistical significance was defined as p value of less than 0.05.

RESULTS

Descriptive Statistics and Propensity Score Matching

A total of 7674 surgical procedures, each from a unique patient, met inclusion criteria for the cohort (Fig. 1).

The mean age was 62.8 years, and 44.6% were female. Baseline comorbidities were common (Table 1), as expected for this high-risk cohort. The most common surgical procedures were abdominal/gastrointestinal, brain, and urologic; 68.4% of patients had an ASA score of 3 and 11.8% had an ASA score of 4 or 5 (Supplemental Table 1, http://links.lww.com/CCX/B323). The mean anesthesia duration was 395 minutes, and greater than 95% of subjects were admitted to the ICU within 2 hours of the end of the surgical procedure (Supplemental Table 1, http://links.lww.com/CCX/B323).

There were 247 subjects exposed to ICIs and 7427 subjects were not exposed. Of the 247 subjects exposed to ICIs, 151 were exposed to nivolumab, 77 were exposed to pembrolizumab, three were exposed to cemiplimab, ten were exposed to durvalumab, six were exposed to atezolizumab, 19 were exposed to ipilimumab, and ten were exposed to relatlimab. Within the ICI-exposed group, 218 subjects were exposed to one ICI and 29 were exposed to two ICIs.

A comparison of baseline preoperative and operative characteristics between the ICI-exposed and nonexposed groups are shown on Table 1; and Supplemental Table 1 (http://links.lww.com/CCX/B323). Baseline characteristics differed between groups in the unmatched cohort. Subjects exposed to ICIs tended to be older and male and to have longer anesthesia time. The specific types of cancers identified in the ICI group were consistent with its approved indications; other types of cancer were more prevalent in the nonexposed group. Preoperative exposure to all subclasses of chemotherapeutic agents was more common in the ICI-exposed group. Congestive heart failure, valvular heart disease, obstructive sleep apnea, peripheral vascular disease, renal failure, obesity, and electrolyte disorders tended to be more common in the group that was not exposed to ICIs.

After matching subjects on the propensity for ICI exposure based on baseline preoperative and operative covariates, 50 of the exposed subjects (20.2%) were not able to be matched. Of the remaining 197, 193 (78.1%) were matched to four nonexposed, 1 (0.4%) was matched with two nonexposed, and 3 (1.2%) were matched to one nonexposed subject, resulting in a total matched cohort of 974 subjects. The ICI-exposed and unexposed groups were well-matched by baseline and operative covariates based on absolute standardized differences, except for exposures to platinum-containing agents and taxanes (Table 1; and Supplemental Table 1, http://links.lww.com/CCX/B323). These two unbalanced variables were included in the conditional regression models for adjustment.

Primary Outcome and Its Subdomains

The composite primary outcome of postoperative cardiopulmonary instability and organ injury was common in both groups. Among the 197 subjects in the ICI-exposed group, 70 (35.5%) developed the primary outcome: 26 (13.2%) experienced cardiac instability, 37 (18.8%) pulmonary instability, 39 (19.8%) kidney injury, and 22 (11.2%) myocardial injury. Of the 777 subjects in the nonexposed group, 251 subjects (32.3%) developed the composite primary outcome: 62 (8.0%) experienced cardiac instability, 129 (16.6%) pulmonary instability, 135 (17.4%) kidney injury, and 48 (6.2%) myocardial injury. Results from conditional logistic regression models showed no statistically significant difference between the ICI-exposed group and the nonexposed group in the odds of the composite primary outcome (OR, 1.12; 95% CI, 0.80–1.58; **Fig. 2**).

The associations between ICI exposure and the primary outcome for prespecified subgroups by age, sex, cancer type, and surgical procedure are shown on **Figure 3**. There was some heterogeneity in point estimates for the primary outcome among these subgroups; however, the relation between ICI exposure and outcome was not statistically significant for any of these subgroups (Fig. 3). Some heterogeneity in point estimates was also noted for subgroups by type of ICI exposure; however, a significant association between ICI exposure and the primary outcome was not observed for either PD-1 inhibitor—pembrolizumab (OR, 1.08; 95% CI, 0.56–2.07) or nivolumab (OR, 0.97; 95% CI, 0.63–1.51) or those exposed to a combined subgroup that included PD-L1 inhibitors, CTLA-4 inhibitors, and LAG-3 inhibitors combined (OR, 2.04; 95% CI, 0.99–4.20).

Secondary Outcomes

Risk of the secondary outcome of prolonged pressor dependence was significantly higher in ICI-exposed

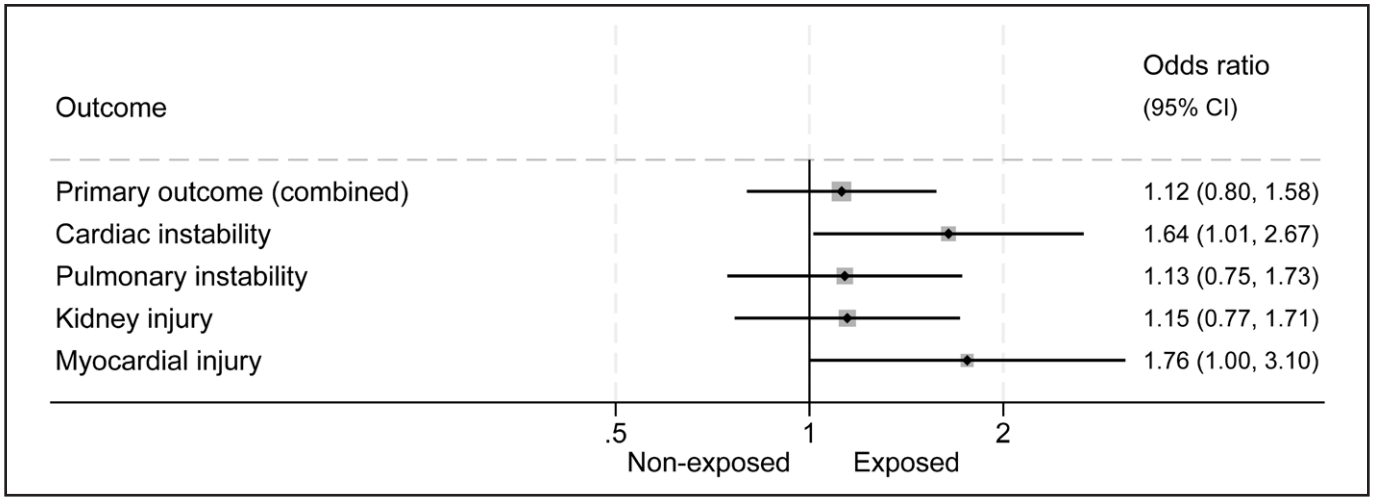

Figure 2. Association of preoperative immune checkpoint inhibitor treatment with postoperative cardiopulmonary instability and organ injury.

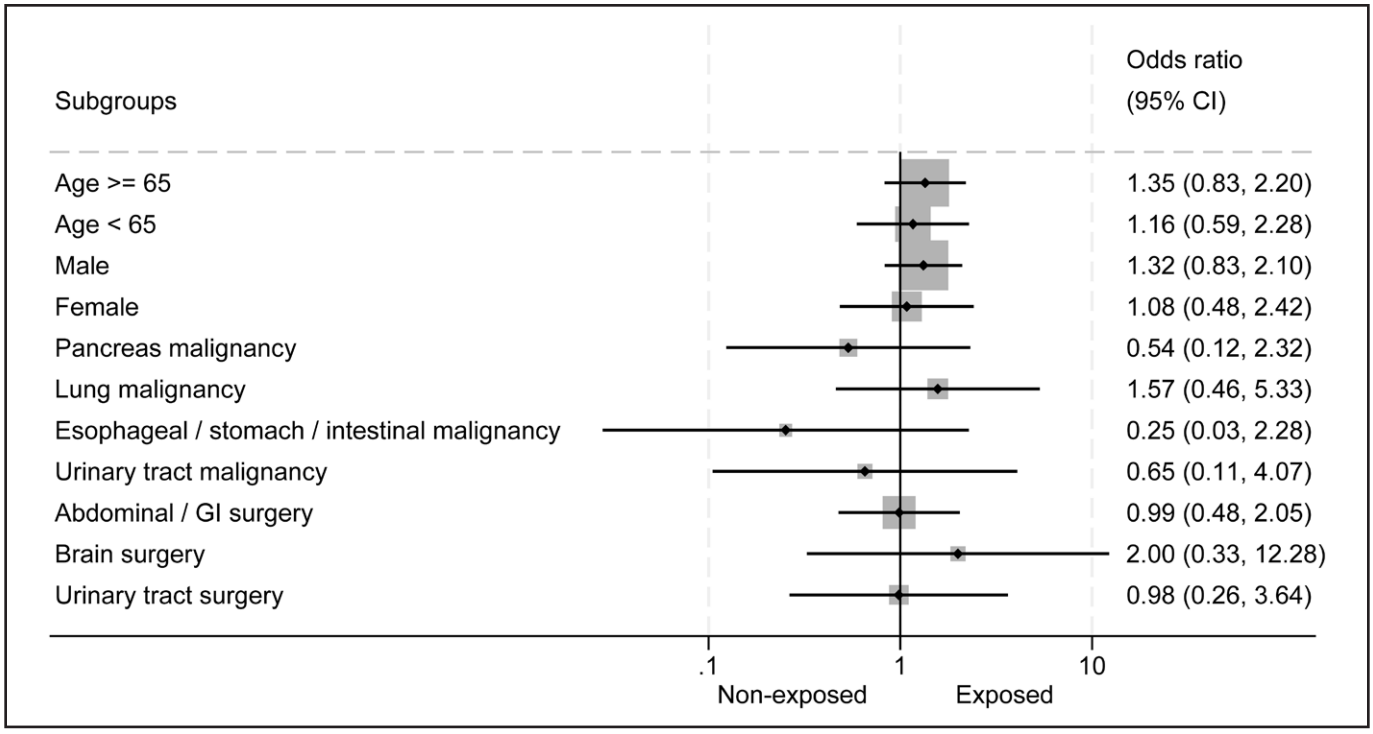

Figure 3. Association between immune checkpoint inhibitor exposure and the composite outcome among prespecified subgroups by age, sex, cancer, and surgical procedure. GI = gastrointestinal.

subjects (OR, 1.64; 95% CI, 1.01–2.67; Fig. 2). Risks of oxygen dependence (OR, 1.13; 95% CI, 0.75–1.73), kidney injury (OR, 1.15; 95% CI, 0.77–1.71), and myocardial injury (OR, 1.76; 95% CI, 1.00–3.10) were not significantly different.

During the hospital stay, five subjects of 197 (2.54%) in the exposed group died within 30 days after surgery compared with 13 of 777 (1.67%) in the nonexposed group. Time from surgery to discharge alive from the hospital was not significantly different between groups ($p = 0.62$; **Fig. 4**).

DISCUSSION

In this retrospective cohort study of cancer patients who underwent surgical procedures at high risk for postoperative cardiopulmonary instability and organ injury, we did not identify a statistically significant

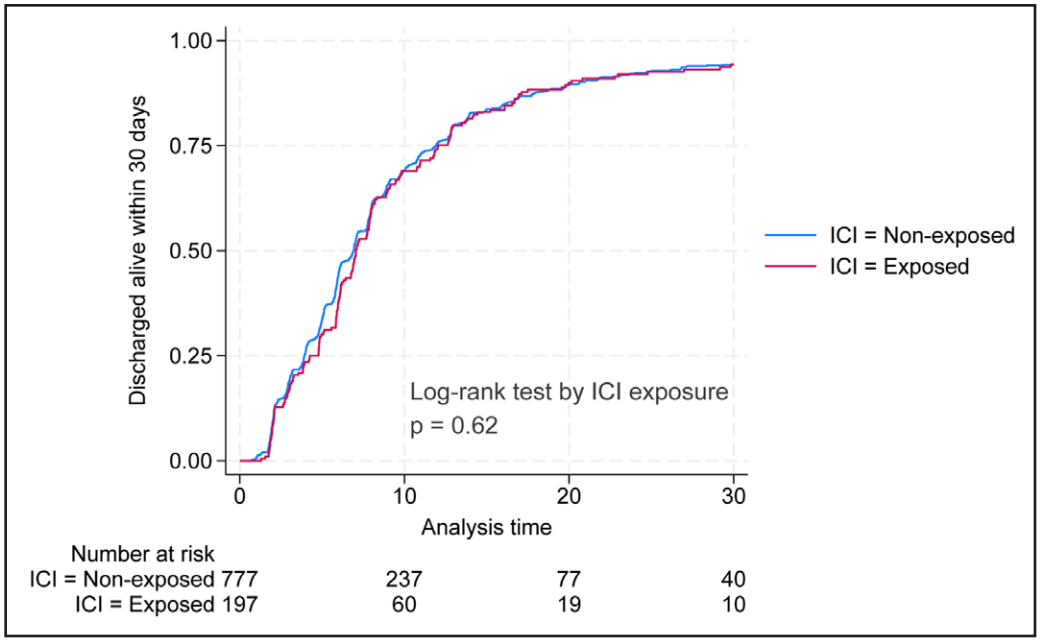

Figure 4. Survival analysis of being discharged alive within 30 d after surgery by immune checkpoint inhibitor (ICI) exposure.

association between ICI exposure within the 6 months before surgery and the composite outcome of cardiopulmonary instability or organ injury after surgery. Risk of the secondary outcome of prolonged pressor dependence was significantly higher in ICI-exposed subjects. We found no significant association between ICI exposure and the secondary outcomes of pulmonary instability, kidney injury, or myocardial injury, although a trend toward higher risk of myocardial injury was noted.

As expected, postoperative cardiopulmonary instability and organ injury were common in this high-risk surgical cohort, occurring in 35.5% and 32.3% of ICI-exposed and nonexposed groups, respectively. The frequency of cardiac instability (prolonged pressor dependence), pulmonary instability (prolonged oxygen dependence), kidney injury (rise in creatinine > 0.3 mg/dL), and myocardial injury (troponin > 0.04 ng/mL) were also in line with expectation and previous reports in high-risk surgical cohorts (22–29).

The ORs for the composite outcome and each of its four components—cardiac instability, pulmonary instability, kidney injury, and myocardial injury—were numerically higher in the ICI-exposed group, however, only the secondary outcome of cardiac instability was statistically significant. The associations between ICI exposure and secondary outcomes should be considered exploratory. Our study was powered to detect ~50% increase in odds of the primary outcome for the ICI-exposed group. Our study did not find an increase in risk of this magnitude for the primary outcome. A larger study would be needed to detect a clinically significant increase in risk smaller than 50%.

ICIs are well-known to cause a wide range of irAEs that can affect any organ system (7). In the nonsurgical setting, the most commonly affected organs are reported to be skin, gastrointestinal tract, endocrine organs, liver, and lung; however, cardiac, kidney, neurologic, and other organ injuries are also reported (30). The profile of adverse events with the PD-1 inhibitors, nivolumab and pembrolizumab, is reported to be similar (30) and higher than reported after PD-L1 inhibitor therapy (30, 31). We noted some heterogeneity by type of ICI in the point estimates for association with the composite outcome of cardiopulmonary instability and organ injury; however, none of these associations were statistically significant. These subgroup analyses were exploratory with small sample sizes and should be interpreted with caution.

Two recently published randomized clinical trials examined the effect of neoadjuvant PD-1 inhibitor treatment on pathologic response and progression-free survival for resectable nonsmall cell lung cancer (2, 3). Both studies reported significant improvements in pathologic response and progression-free survival in the groups treated with PD-1 inhibitors at 24-month follow-up. No safety signal with PD-1 treatment was reported during the overall duration of either trial; however, the frequency of perioperative adverse events, including sepsis, respiratory insufficiency/infection, pulmonary embolism, and death, were numerically higher with PD-1 inhibitor therapy in both trials. We also observed a numerically higher frequency of 30-day mortality in the ICI-exposed group in our study, but deaths were infrequent in both groups.

Given improved long-term survival from neoadjuvant PD-1 inhibitor treatment in lung and other cancers, clinicians can reasonably expect to see more patients presenting for postoperative critical care after exposure to ICIs. The potential for short-term postoperative complications, particularly cardiac complications, from ICI treatment cannot be excluded by this study.

There are several limitations of this study. We were not able to determine the exact indication for ICI use in each subject or the duration of treatment with ICIs or chemotherapeutic agents for cancer. We also did not have information on the total dose of ICI or occurrence of ICI related irAEs before surgery. The vast majority of subjects in this study were exposed to a PD-1 inhibitor, and we did note some heterogeneity in point estimates for risk of adverse outcome by type of ICI; thus, our results might not generalize to all ICIs. Furthermore, our study was conducted in a cohort admitted to the ICU after surgery and at high risk for postoperative cardiopulmonary instability. Thus, results of this study may not generalize to a lower risk cohort exposed to ICIs before surgery. We note that baseline comorbidities and treatment with standard cancer chemotherapeutics differed between ICI-exposed and control groups. We attempted to control for confounding with propensity score matching, and addressed the unbalanced variables by including them in the regression model. However, like all observational studies, we cannot address confounding factors that were not measured. Therefore, the potential for residual confounding remains.

CONCLUSIONS

Exposure to ICIs within 6 months before high-risk surgery was not significantly associated with the composite primary outcome of postoperative cardiopulmonary instability or organ injury or the secondary outcome of time to hospital discharge. A signal toward increased risk of cardiac instability and injury was noted. Our study was not powered to detect an increase in risk smaller than 50%. Considering the long-term benefits of neoadjuvant ICI therapy and the increasing prevalence of its use, larger studies are needed to clarify the risks of ICI exposure on short-term postoperative outcomes, particularly cardiac complications, in surgical patients.

1 *Department of Anesthesiology, Mackay Memorial Hospital, Taipei, Taiwan.*

2 *Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD.*

3 *Department of Anesthesiology/Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.*

4 *Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Dr. Faraday contributed to the conception of this work. Drs. Tang and Faraday designed the study. Dr. Bergmann performed data acquisition and curation. Dr. Tang conducted formal analysis. Drs. Tang and Faraday interpreted the data. Drs. Tang and Faraday contributed to writing the original draft. Drs. Bergmann, Vaidya, and Faraday contributed to reviewing the study results and editing of the writing. This final version of this article is read and approved by all authors.

This study was supported by the Department of Anesthesiology/Critical Care Medicine at the Johns Hopkins University School of Medicine.

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: nfaraday@jhmi.edu

REFERENCES

1. Vaddepally RK, Kharel P, Pandey R, et al: Review of indications of FDA-approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence. *Cancers* 2020; 12:738
2. Wakelee H, Liberman M, Kato T, et al: Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med* 2023; 389:491–503
3. Provencio M, Nadal E, González-Larriba JL, et al: Perioperative nivolumab and chemotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2023; 389:504–513
4. Chocarro L, Bocanegra A, Blanco E, et al: Cutting-edge: Preclinical and clinical development of the first approved LAG-3 inhibitor. *Cells* 2022; 11:2351
5. Gaikwad S, Agrawal MY, Kaushik I, et al: Immune checkpoint proteins: Signaling mechanisms and molecular interactions in cancer immunotherapy. *Semin Cancer Biol* 2022; 86:137–150
6. Ceschi A, Noseda R, Palin K, et al: Immune checkpoint inhibitor-related cytokine release syndrome: Analysis of WHO global pharmacovigilance database. *Front Pharmacol* 2020; 11:557
7. Kennedy LB, Salama AKS: A review of cancer immunotherapy toxicity. *CA Cancer J Clin* 2020; 70:86–104
8. Patrinely JR Jr, Johnson R, Lawless AR, et al: Chronic immune-related adverse events following adjuvant anti–PD-1 therapy for high-risk resected melanoma. *JAMA Oncol* 2021; 7:744–748
9. Keung EZ, Ukponmwan EU, Cogdill AP, et al: The rationale and emerging use of neoadjuvant immune checkpoint blockade for solid malignancies. *Ann Surg Oncol* 2018; 25:1814–1827

10. Helmink BA, Roland CL, Kiernan CM, et al: Toxicity of immune checkpoint inhibitors: Considerations for the surgeon. *Ann Surg Oncol* 2020; 27:1533–1545
11. Elias AW, Kasi PM, Stauffer JA, et al: The feasibility and safety of surgery in patients receiving immune checkpoint inhibitors: A retrospective study. *Front Oncol* 2017; 7:121
12. Bott MJ, Cools-Lartigue J, Tan KS, et al: Safety and feasibility of lung resection after immunotherapy for metastatic or unresectable tumors. *Ann Thorac Surg* 2018; 106:178–183
13. Gyorki DE, Yuan J, Mu Z, et al: Immunological insights from patients undergoing surgery on ipilimumab for metastatic melanoma. *Ann Surg Oncol* 2013; 20:3106–3111
14. Amaria RN, Reddy SM, Tawbi HA, et al: Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. *Nat Med* 2018; 24:1649–1654
15. Blank CU, Rozeman EA, Fanchi LF, et al: Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. *Nat Med* 2018; 24:1655–1661
16. Carthon BC, Wolchok JD, Yuan J, et al: Preoperative CTLA-4 blockade: Tolerability and immune monitoring in the setting of a presurgical clinical trial. *Clin Cancer Res* 2010; 16:2861–2871
17. Forde PM, Chaft JE, Smith KN, et al: Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med* 2018; 378:1976–1986
18. Moore BJ, White S, Washington R, et al: Identifying increased risk of readmission and in-hospital mortality using hospital administrative data: The AHRQ elixhauser comorbidity index. *Med Care* 2017; 55:698–705
19. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). 2023. Available at: https://www.nccn.org/guidelines/category_1. Accessed November 1, 2023
20. Austin PC: An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; 46:399–424
21. Austin PC: Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat - Simul Comput* 2009; 38:1228–1234
22. Mokart D, Giaoui E, Barbier L, et al: Postoperative sepsis in cancer patients undergoing major elective digestive surgery is associated with increased long-term mortality. *J Crit Care* 2016; 31:48–53
23. Singh G, Gladdy G, Chandy TT, et al: Incidence and outcome of acute lung injury and acute respiratory distress syndrome in the surgical intensive care unit. *Indian J Crit Care Med* 2014; 18:659–665
24. Serpa Neto A, Hemmes SNT, Barbas CSV, et al; PROVE Network investigators: Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: A systematic review and meta-analysis. *Lancet Respir Med* 2014; 2:1007–1015
25. Oh TK, Song I-A, Kim SJ, et al: Hyperchloremia and postoperative acute kidney injury: A retrospective analysis of data from the surgical intensive care unit. *Crit Care* 2018; 22:277–275
26. Oh TK, Song I-A, Jeon Y-T: Admission to the surgical intensive care unit during intensivist coverage is associated with lower incidence of postoperative acute kidney injury and shorter ventilator time. *J Anesth* 2019; 33:647–655
27. Grams ME, Sang Y, Coresh J, et al: Acute kidney injury after major surgery: A retrospective analysis of Veterans health administration data. *Am J Kidney Dis* 2016; 67:872–880
28. Devereaux PJ, Chan MTV, Alonso-Coello P, et al; Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; 307:2295–2304
29. Yu J, Lim B, Lee Y, et al: Risk factors and outcomes of myocardial injury after non-cardiac surgery in high-risk patients who underwent radical cystectomy. *Medicine (Baltimore)* 2020; 99:e22893
30. Ji HH, Tang XW, Dong Z, et al: Adverse event profiles of anti-CTLA-4 and anti-PD-1 monoclonal antibodies alone or in combination: Analysis of spontaneous reports submitted to FAERS. *Clin Drug Investig* 2019; 39:319–330
31. Banna GL, Cantale O, Bersanelli M, et al: Are anti-PD1 and anti-PD-L1 alike? The non-small-cell lung cancer paradigm. *Oncol Rev* 2020; 14:490