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Postoperative acute respiratory distress syndrome in patients with previous exposure to bleomycin

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Abstract

Objective—To determine the incidence and risk factors for postoperative acute respiratory distress syndrome (PO-ARDS) in a large cohort of bleomycin-exposed patients undergoing surgery with general endotracheal anesthesia.

Patients and Methods—From a Mayo Clinic cancer registry, we identified patients who had received systemic bleomycin (n=1120) and then underwent a major surgical procedure requiring >1 hour of general anesthesia between January 1, 2000 and August 30, 2012. Heart/lung/liver transplants were excluded. PO-ARDS (within seven days after surgery) was defined according to Berlin criteria.

Results—We identified 316 patients who underwent 541 major surgical procedures. Only 7 patients met criteria for PO-ARDS; all were Caucasian males, and 6 were current or former smokers. On univariate analysis, we observed an increased risk for PO-ARDS in patients who were current or former smokers. Furthermore, there was significantly greater crystalloid and colloid administration in patients with PO-ARDS. We also observed a trend toward longer surgical duration and red blood cell transfusion in patients with PO-ARDS, though this was not significant. Intraoperative FiO₂ was not associated with PO-ARDS. In bleomycin-exposed patients, the incidence of PO-ARDS following major surgery under general anesthesia is approximately 1.3% (C.I. 0.6–2.6%). For first major procedures after bleomycin, the incidence is 1.9% (C.I. 0.9–4.1%).

Conclusions—The risk for PO-ARDS in patients exposed to systemic bleomycin appears to be lower than expected. Smoking status may be an important factor modifying risk for PO-ARDS in these patients.

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Introduction

Bleomycin is an anti-tumor antibiotic highly effective in the treatment of testicular carcinomas, lymphomas, squamous cell carcinomas and Kaposi's sarcoma.¹ It was originally isolated from the yeast *Streptomyces verticillus* in 1966 and it works by breaking the DNA double helix through production of free radicals.² Since the early days of its use, the most serious adverse effect of bleomycin therapy is pulmonary toxicity which manifests acutely in 10–40% with non-specific symptoms such as dyspnea, tachypnea and non-productive cough.³ Typical bleomycin regimens used for cancer therapy may lead to pneumonitis,⁴ pulmonary fibrosis,^{5,6} and impairment of pulmonary function.^{7,8} The overall mortality of bleomycin-associated pulmonary toxicity is estimated to range from 1–2%.^{9–12}

In this context, perioperative management of patients with previous exposure to bleomycin can be challenging due to the compounded risk of postoperative pulmonary complications.^{13,14} Over three decades of human and animal investigations have sought strategies to mitigate this risk. This includes conservative crystalloid administration and ventilator strategies including limitation of the administered fraction of inspired oxygen (FiO₂). Evidence supporting this practice originated in a study by Goldiner *et al.* in the late 1970's describing 5 bleomycin-exposed patients who received an average intraoperative FiO₂ of 0.39 during surgery and subsequently developed fatal postoperative acute respiratory distress syndrome (ARDS). The same report described a subsequent cohort of 12 patients of whom average intraoperative FiO₂ was limited to 0.24, and fluid administration favored a greater proportion of colloid rather than crystalloid solutions. Within this group, there were no postoperative pulmonary complications and all patients survived.¹⁴ Ensuing case reports extended the concern of perioperative oxygen toxicity in surgical patients.^{15,16}

In the early 1980's, several animal studies determined that interstitial fibrosis was the major pathologic manifestation of oxygen toxicity following bleomycin exposure.^{17–20} Taken together, the human and animal studies led to the long-standing recommendation that anesthesia providers administer intraoperative FiO₂ as low as tolerated for bleomycin-exposed patients. Similarly, fluid replacement strategies based on colloids over crystalloids have been routinely favored in these patients.¹³

While it is generally accepted that oxygen toxicity is a risk in bleomycin-exposed surgical patients, not all studies have supported the practice of limiting FiO₂ administration in surgical patients.^{13,21} Along these lines, it is reasonable to postulate that there are risks with severe FiO₂ restriction in all surgical patients (i.e., infection, wound healing²²), but especially in patients with pre-existing interstitial lung disease who are at greater risk of perioperative hypoxemia. With this information as background, the objective of this study was to determine the incidence of postoperative acute respiratory distress syndrome (PO-ARDS) in a large cohort of patients with previous systemic bleomycin exposure undergoing major surgery requiring >1 hour of general anesthesia. Furthermore, we aimed to identify preoperative, intraoperative, and postoperative risk factors associated with PO-ARDS.

Methods

Institutional review board approval was obtained through the Mayo Clinic health system. Minnesota State law requires a general authorization to review medical records for research. Patients who receive care at Mayo Clinic can “opt out” of this authorization if they desire. For the present investigation, all included participants had authorized the use of their medical record for research.

Data were collected from three primary sources: 1) the Perioperative DataMart, 2) Mayo Clinic Life Science Services and the Data Discovery Query Builder (MCLSS/DDQB), and 3) The Mayo Clinic Cancer Registry. A detailed description of the data extraction capabilities of DataMart and MCLSS/DDQB can be found in previous reports by this institution.²³ Specific variables extracted from the Perioperative DataMart included the following: height, weight, age, date of birth, gender, and body mass index (BMI). BMI was calculated from the most recent height and weight documented before the surgical procedure. All details related to the surgical procedure, anesthesia start and stop times, surgery start and stop times, and American Society of Anesthesiologists (ASA) patient classification score were also collected from the Perioperative DataMart.^{24,25} For the present investigation, categories of data collected from this resource included baseline comorbidities, preoperative laboratory values, and medications being taken at the time of the surgical procedure.

The overall data collection strategy is depicted in figure 1. An extensive search of all Mayo Clinic patients with a history of systemic (i.e., non-topical) bleomycin exposure was conducted using the Mayo Clinic Cancer Registry and MCLSS identifying 1,120 unique patients. MCLSS/DDQB was then used to identify which of these patients underwent surgical procedures between January 2000 (advent of the electronic intraoperative anesthesia record) and August, 2012. Procedures were required to occur after the final dose of bleomycin. Within this cohort of bleomycin-exposed patients there were 960 procedures. Minor procedures lasting less than 1 hour and those that did not require endotracheal intubation were subsequently excluded (n=411). All heart, lung, and liver transplants were also excluded (n=3). These transplant procedures were excluded due to presumed left atrial hypertension in cardiac transplant patients, the confounding variable of pulmonary reimplantation response in lung transplant surgery²⁶ as well as the historically high risk of ARDS with liver transplant surgery.^{27,28} Minor, non-invasive procedures were excluded because it has been reported that PO-ARDS in bleomycin exposed patients is associated with surgical acuity.²⁹ A database was created to catalog baseline demographic and clinical characteristics, as well as preoperative, intraoperative, and postoperative parameters that have been identified as risk factors/modifiers for PO-ARDS.²³ Patients with incomplete records were included to the best extent possible. For instance, because of the large number of surgical referrals from outside providers, there was limited data on the total dose of bleomycin that the patients received.

Comorbid conditions were considered present if a physician documented the diagnosis in the electronic medical record within the 5-yr interval prior to the date of the surgical procedure. Medications were considered present if documented in the list of current medications for the

patient at the time of hospital admission, limited to 90 days prior to admission (6 months for chemotherapy). Smoking status was categorized as current, past, or never smoked.

Outcome Variables

The primary outcome variable was the development of ARDS within 7 days of the surgical procedure. The 2012 Berlin Definition was used for the determination of ARDS to reflect contemporary clinical nomenclature.³⁰ Specifically, ARDS was defined as hypoxemic respiratory insufficiency with acute onset, arterial oxygen tension/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 300 mm Hg with the presence of new bilateral pulmonary infiltrates on chest radiograph and the absence of left atrial hypertension as the primary explanation of the hypoxemia and chest radiograph findings. The severity of PO-ARDS was classified as follows: Mild, 200 mm Hg < $\text{PaO}_2/\text{FiO}_2$ < 300 mm Hg with positive end expiratory pressure (PEEP) or CPAP (continuous positive airway pressure) ≥ 5 cm H_2O ; Moderate, 100 mm Hg < $\text{PaO}_2/\text{FiO}_2$ < 200 mm Hg with PEEP ≥ 5 cm H_2O ; Severe, $\text{PaO}_2/\text{FiO}_2$ < 100 mm Hg with PEEP ≥ 5 cm H_2O .³⁰ If a patient received non-invasive ventilatory assistance (bipap (bilevel positive airway pressure)) then severity was classified as mild. The adjudication of ARDS was determined using a two-step process. First, a previously validated electronic surveillance system screened all study participant's electronic health records for ARDS by evaluating all arterial blood gas (ABG) results and chest radiograph reports.^{23,24} Specifically, if the arterial blood gas noted a $\text{PaO}_2/\text{FiO}_2$ < 300 mm Hg and a chest radiograph report contained the key terms "bilateral infiltrates" and/or "edema" within 24 hours of the qualifying ABG, the study participant was considered screen positive. All screen positive cases were then independently reviewed by two study investigators (A.S., G.W.). Disagreements between the two initial adjudicators were resolved by a third investigator experienced in the study of ARDS (DJK). In a validation cohort the DDQB tool used for data extraction achieved a sensitivity ranging from 91% to 100%, and a specificity ranging from 98% to 100%.^{23,24} Thus, all study participants who screened negative were adjudicated as not having developed ARDS. Procedures were excluded from this study if adjudicators determined that there was evidence for preexisting ARDS (n=5). Therefore, the total exclusions were short procedures (411) + transplants (3) + pre-existing ARDS criteria (5) to equal 419 procedures. Secondary outcome variables included in-hospital mortality, hospital length of stay and invasive ventilator days.

Statistical analysis

Continuous data were expressed as median (interquartile range) and the Wilcoxon rank sum test was utilized for statistical hypothesis testing. Differences in categorical variables were assessed with the Fisher's exact test. $P < 0.05$ was considered statistically significant. All statistical analyses were done using JMPTM 9.0.1 statistical software (SAS Institute, Inc., Cary, North Carolina, USA). Only the first procedure after bleomycin was included in the risk factor analysis (N=316) with a single exception. One patient had PO-ARDS following his 6th qualifying procedure. In this case, the patient's 5 previous surgeries were excluded.

Results

A total of 541 procedures in 316 unique patients (81 female) met criteria for inclusion in this study. The most common indications for bleomycin were testicular carcinoma (44%, n=140), Hodgkin's lymphoma (31%, n=98) and non-Hodgkin's lymphoma (18%, n=57). There were 7 cases of PO-ARDS, all of which involved Caucasian males; 6 were current or former smokers. The median age was 45 (absolute range 28–63).

All but a single case of PO-ARDS occurred following the 1st procedure after bleomycin exposure. The one exception was also the only postoperative fatality. This involved a 50 year-old gentleman undergoing a left total hip arthroplasty re-implantation, his 6th procedure after bleomycin. The intraoperative course was unremarkable; however in the post anesthesia care unit he suffered cardiopulmonary arrest. Resuscitation using advanced cardiac life support protocols successfully restored a perfusing rhythm but he later arrested again in the intensive care unit (ICU) resulting in significant hypoxia. The patient then returned to the operating room for emergent cardiectomy to explore and treat a massive pulmonary embolism but no pulmonary thrombus was found. He was subsequently placed on extracorporeal membrane oxygenation but ultimately expired following a transition to comfort care measures.

The other 6 patients with PO-ARDS required postoperative ICU admission. A brief demographic description including procedure and smoking status for each PO-ARDS case is included in table 1. The patients with “mild” PO-ARDS were either on bipap (patient 3) or intubated with a PaO₂/FiO₂ ratio classified as mild (patients 4, 7). Baseline demographic characteristics and the distribution of perioperative ARDS risk factors/modifiers among those who did and did not develop PO-ARDS (first procedure only) after bleomycin are presented in table 2. Median age, ASA status and BMI were similar between the group suffering PO-ARDS and the group without PO-ARDS. Regarding intraoperative data, the total volume of crystalloid administered and colloid infusion rate (ml/kg/hr) were associated with increased risk for PO-ARDS (p<0.05). The duration of anesthesia was longer and red blood cells were transfused more often in those who developed postoperative ARDS; however, these associations did not meet statistical significance. Mean FiO₂, rate of crystalloid administration (ml/kg/hr), total volume of colloid administration as well as total fluid balance ((crystalloid + colloid) / (EBL + urine output)) were not associated with increased risk for PO-ARDS. Total cumulative bleomycin dose did not predict PO-ARDS, although the availability of this data was incomplete. For months from last dose of bleomycin we included a subgroup analysis excluding the patient who had PO-ARDS after his 6th qualifying procedure. This is included in table 2.

For the secondary outcomes of interest, hospital length of stay, ICU admission rate and invasive ventilator days were significantly greater in patients with PO-ARDS (table 3). Furthermore, the number of ICU-free days within one month after surgery was less in those patients with PO-ARDS. Mortality trended higher for patients with PO-ARDS but this did not reach statistical significance.

Discussion

Cancer treatment with bleomycin increases the lifetime risk of pulmonary dysfunction.³¹ The major finding of this study is that the incidence of PO-ARDS in bleomycin-exposed patients undergoing general endotracheal anesthesia for surgical procedures lasting greater than 1 hour was considerably lower than expected. In total, we observed 7 cases of PO-ARDS in 316 bleomycin treated patients undergoing 541 procedures. Therefore, if one considers all procedures as the denominator, we conclude that the overall incidence of PO-ARDS in bleomycin-exposed patients undergoing a procedure that fits our inclusion criteria is approximately 1.3% (C.I. 0.6–2.6%). If one considers only the patient's first qualifying procedure following bleomycin, the incidence of PO-ARDS is approximately 1.9% (C.I. 0.9–4.1%).

The large dataset provides the first estimate of an incidence of PO-ARDS in patients undergoing a major surgery under general anesthesia after receiving bleomycin. In the general surgical population (without bleomycin exposure), the incidence of PO-ARDS is estimated to be 0.2%.³² Importantly, that report excluded high risk surgical procedures such as cardiac, thoracic, vascular, trauma, and transplant.³² A previous study from our institution that included higher acuity cases reported that the overall incidence of PO-ARDS (within the first 5 postoperative days) in all patients undergoing more than 3 hours of general anesthesia was 2.6% (113/4281).²³ This same study showed the incidence of PO-ARDS in aortic vascular, cardiac, and thoracic surgery is 6.2, 5.0, and 2.9%, respectively. In the current study, we included these higher acuity procedures and found a lower incidence of PO-ARDS, confirming that the incidence of PO-ARDS in bleomycin-exposed patients is quite low.

Nygaard *et al.* was the first to describe postoperative respiratory failure in patients treated preoperatively for esophageal cancer with bleomycin and 3000 rads of radiation.²⁹ The authors observed death from respiratory failure in three of eight patients following esophageal resection 5–6 weeks after bleomycin. The idea of oxygen restriction was first purported by Goldiner *et al.* and has since become common practice based largely on animal studies and a few additional human studies, including a report from this institution.^{16,33} In the meantime, several studies have questioned the practice of severe oxygen restriction.^{13,21,34} For example, in the largest study to date, Donat *et al.* examined 77 bleomycin-exposed patients undergoing 97 major procedures over an 8-year span, and found that postoperative pulmonary complications did not depend on intraoperative FiO₂ (0.39 in the pulmonary complication group (n=19) vs. 0.41 in the non-pulmonary complication group (n=58). Moreover, excessive crystalloid administration was shown to be a greater contributor to postoperative respiratory failure and their conclusion was that perioperative oxygen restriction is not necessary.¹³

More recently, Wuethrich *et al.* showed that three minute preoxygenation with 100% FiO₂ and a target average intraoperative FiO₂ of 30% was safe in a retrospective study of 47 bleomycin-exposed patients who underwent retroperitoneal lymph node dissection. Their conclusion was that restriction of oxygen may subject patients to unnecessary operative risk including hypoxemia.³⁴ Interestingly, a group of investigators from Duke University

Medical Center reported their experience on the administration of therapeutic hyperbaric oxygen to bleomycin-exposed patients.³⁵ No pulmonary consequences were identified among the 15 patients evaluated, further challenging the need for oxygen restriction perioperatively.

In this context, the second major aim of this study was to identify modifiable and non-modifiable perioperative risk factors for PO-ARDS. Previous identified risk factors include: patients over age 70,^{36–38} cumulative bleomycin dose >450U,^{36–38} previous pulmonary irradiation,^{39,29} impairment of renal function,⁴⁰ smoking,⁴¹ trans-operative volume replacement,^{13,42} duration of surgery,¹³ hyperoxia^{14–16,43} and blood transfusion.¹³ In the present study, the univariate analyses identified associations between smoking status, and volume and rate of fluid administration and PO-ARDS. Interestingly, while bleomycin-associated pulmonary toxicity in general is dose-dependent, none of the patients in our registry received a cumulative dose of bleomycin that was greater than 360 units. The drug currently carries a black box warning that cumulative doses should not exceed 400 units. Regarding our secondary outcomes, it is not surprising that ICU and hospital length of stay were longer in the PO-ARDS cohort. There were more in-hospital deaths for the non-ARDS cohort, likely attributable to the larger sample size. The expected mortality for mild, moderate and severe ARDS is 27%, 35% and 45%.³⁰ We observed 3 cases of mild ARDS and 4 cases of severe ARDS but only one in-hospital death, for an overall ARDS mortality rate of 14%. Reasons for this low mortality are difficult to discern based on the small number of patients with PO-ARDS.

The major limitation of our case-control study is the challenge of meaningful statistical analysis of perioperative risk factors when the incidence of cases (PO-ARDS) was considerably lower than expected, leaving it underpowered to assess relationships between risk factors and outcome. Furthermore, because of the limited number of PO-ARDS cases we included a patient whose PO-ARDS occurred after his 6th qualifying procedure. We do not believe this choice for the procedure in control patients would result in any potential bias with the possible exception of time (months) since last bleomycin administration. Interestingly, this patient was one of two cases that had bleomycin exposure >20 years prior to developing PO-ARDS. Importantly, we repeated the analysis for the comparison of time since last bleomycin administration with the patient who developed PO-ARDS following their 6th procedure excluded. We found that by excluding this case, the median time was not significantly different from the non-ARDS controls. While our study did not refute the dogma that bleomycin poses a lifetime risk of pulmonary morbidity, we feel that the re-analysis suggests the risk of PO-ARDS does not *increase* over time. Our data also suggest that the duration of anesthesia, estimated blood loss, and need for RBC transfusion may be associated with postoperative ARDS, but statistical significance was lacking.

The limited number of ARDS cases may lead to type II error for other associations as well. For example, the mean intraoperative FiO₂ was slightly higher for patients with PO-ARDS. One possible explanation for this observation was that patients with PO-ARDS were simply more sick and at higher risk independent of bleomycin. Notably, of the 7 patients with PO-ARDS, 2 had intraabdominal sepsis, 2 underwent major vascular surgery and one had cardiopulmonary arrest in the post anesthesia care unit. It is well established that sepsis, and

major vascular surgery are risk factors for PO-ARDS suggesting that some of these patients may have developed PO-ARDS regardless of their bleomycin history.^{29,43}

A key question is what implications do these findings have for perioperative management of bleomycin-exposed patients? Several contemporary principles and practices have been implemented since the review by Waid-Jones and Coursin.³ Namely, it is generally accepted that changes in ventilator management over the last decade have reduced PO-ARDS in all patients.³³ In the past, high FiO₂ was administered with zero PEEP and high tidal volume. Lung injury that was attributed to high FiO₂ may indeed have been caused by volutrauma and atelectrauma. We believe that the low incidence of PO-ARDS in our patient population is at least in part related to practice changes in intra-operative ventilator management at our institution. Based on these specialty-wide practice trends, our findings may be generalizable for other institutions with similar ventilator strategies,^{33,44}

A recent meta-analysis of intraoperative ventilator strategies to prevent postoperative pulmonary complications found the use of lower tidal volumes, higher levels of PEEP and/or recruitment maneuvers have the potential to protect against postoperative pulmonary complications.⁴⁵ While the risk of oxygen toxicity must be considered in bleomycin-exposed patients, there is no evidence to support severe FiO₂ restriction (i.e., limiting FiO₂ to below 0.3). Additional studies addressing these issues will require a larger population and likely multicenter collaboration with a greater number of PO-ARDS occurrences in bleomycin-exposed patients.

Conclusion

The most serious and limiting side effect from bleomycin is acute pulmonary toxicity. Furthermore, it has traditionally been considered to impose a lifelong risk of postoperative lung injury. In a large cohort of patients receiving major surgery under general endotracheal anesthesia, we analyzed over a decade of intraoperative electronic medical records with validated search algorithms to reveal that the incidence of PO-ARDS was considerably lower than expected. We observed an increased risk for PO-ARDS in patients who were current or former smokers. There was significantly greater crystalloid and colloid administration, and a trend toward longer surgical duration and red blood cell transfusion in patients with PO-ARDS. While this study did not refute the dogma that bleomycin poses a lifetime risk of pulmonary complications, the low incidence of PO-ARDS in this report may be related to practice changes in intra-operative ventilator management, conservative fluid and transfusion strategies, and overall dosage of bleomycin. Because other variables such as FiO₂ were not ruled-out as modifiable risk variables, additional trials will require a larger trial of bleomycin exposed patients.

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Alphabetical list of abbreviations

ABG	Arterial blood gas
ARDS	Acute respiratory distress syndrome
ASA	American society of anesthesiologists
BMI	Body mass index
FiO₂	Fraction of inspired oxygen
ICU	Intensive care unit
MCLSS/DDQB	Mayo clinic life sciences services/data discovery query builder
PaO₂	Partial pressure of arterial oxygen
PEEP	Positive end expiratory pressure
PO-ARDS	Post operative acute respiratory distress syndrome

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Figure 1.

Methods flow diagram. PO-ARDS was determined in 7 out of 541 procedures 1.3% (C.I. 0.6–2.6). Because 1 of the 7 patients developed PO-ARDS after the sixth surgery following bleomycin therapy, the incidence of PO-ARDS associated with the first major procedure after last exposure to bleomycin was 6 out of 315 patients 1.9% (C.I. 0.9–4.1). See text for further explanation. Unless otherwise indicated, n=number of procedures and number of

patients. MCLSS: Mayo Clinic Life Science Services and the Data Discovery Query Builder.

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Table 1

Demographics and procedures for patients with PO-ARDS (n=7)

Age	Smoking	Regimen	Bleomycin Indication	Procedure Associated with Postoperative ARDS	ARDS
28	CS	BEP	Germ Cell Tumor	Right thoracotomy; excision mediastinal mass (6.7 hr)	Severe
50	FS	BEP	Testicular Carcinoma	Left hip arthroplasty revision; irrigation & debridement (2.8 hr)	Severe (Deceased)
63	CS	MACOP-B	Non-Hodgkin's Lymphoma	Left neck dissection with SCM flap for metastatic carcinoma (5.5 hr)	Mild
54	CS	BEP	Testicular Carcinoma	Abdominal exploration; thromboendarterectomy of the proximal infrarenal aorta, aortobifemoral bypass (9.7 hr)	Mild
45	NS	BEP	Testicular Carcinoma	Abdominal exploration: vena cava bypass, vertebral body tumor excision (10.1 hr)	Severe
43	FS	Vanderbt. Protocol	Non-Hodgkin's Lymphoma	Exploratory laparotomy; cholecystectomy in the setting of intraabdominal sepsis (2.3 hr)	Severe
36	CS	BEP	Testicular Carcinoma	Abdominal exploration; washout for neutropenic colitis (2 hr)	Mild

BEP: bleomycin, etoposide, cisplatin; MACOP-B: methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; Vanderbilt Protocol: cyclophosphamide, etoposide, vincristine, doxorubicin, bleomycin, methotrexate, prednisone. CS: current smoker, FS: former smoker, NS: non-smoker. Severity of ARDS was determined in accordance with the Berlin criteria.³⁰ The patients with "mild" PO-ARDS were either on bipap (patient 3) or intubated with a P:F ratio classified as mild (patients 4, 7).

Table 2

Comparison of non-ARDS and ARDS patients (first procedure only)

Characteristic	Non-ARDS (n=309)	ARDS (n=7)	P value
<i>Demographics</i>			
Age (years)	43 (29, 59)	45 (36, 54)	0.92
Male	228 (73.8%)	7 (100%)	0.04
BMI	26.7 (23.8, 31.1)	26.9 (24.4, 28.5)	0.67
ASA	3 (2, 3)	3 (2, 3)	0.24
GERD	29 (9.4%)	1 (14%)	0.51
Diabetes mellitus	19 (6.1%)	0	0.99
COPD	8 (2.6%)	1 (14%)	0.18
ILD	15 (4.8%)	1 (14%)	0.31
Statins w/i 90 days	49 (15.8%)	1 (14%)	0.99
PPI w/i 90 days	74 (24%)	5 (71%)	0.01
Inhaled corticosteroids w/i 90 days	11 (3.6%)	1 (14%)	0.24
ACE-I w/i 90 days	32 (10.4%)	2 (29%)	0.17
ARB w/i 90 days	10 (3.2%)	0	0.99
Emergency Procedure	12 (3.8%)	1 (14%)	0.26
Single lung ventilation	26 (8.4)	1 (14%)	0.47
Current or former smoker	71 (43.6%)	6 (85.7%)	0.01
Months from last bleomycin	2.4 (0, 25.1)	6.8 (2.8, 247)	<0.001[†]
Cumulative bleomycin dose (units)	96 (49.5, 229.5)	140 (40, 240)	0.99
Pre-op hemoglobin	12.2 (10.7, 13.8)	12.3 (10.5, 14.7)	0.92
Pre-op creatinine	1.1 (0.9, 1.3)	0.9 (0.8, 1.4)	0.98
Pre-op albumin (n=134)	4.1 (3.8, 4.3)	3.3 (2.9, 3.7)	0.05
<i>Intraoperative variables</i>			
Anesthesia Duration (hrs)	3.7 (2.2, 5.6)	5.5 (2.3, 9.7)	0.18
Estimated blood loss (ml)	50 (0, 398)	300 (0, 934)	0.14
Red blood cell transfusion (ml)	0 (0, 0)	0 (0, 990)	0.06
Platelet transfusion (ml)	0 (0, 0)	0 (0, 257)	0.34
FFP transfusion (ml)	0 (0, 0)	0 (0, 0)	0.98
Total crystalloid (ml)	2002 (1000, 4256)	2442 (1694, 8400)	0.02
Crystalloid/kg/Hr	7.6 (5.0, 10.8)	11.0 (8.7, 12.1)	0.15
Total colloids (ml)	0 (0, 500)	500 (107, 1500)	0.09
Colloid/kg/hr	0 (0, 1.5)	1.2 (0.4, 5.0)	0.02
Fluid balance	573 (368–804)	621 (478, 690)	0.98
Max tidal volume (n=139)	729 (612, 928)	673 (594, 752)	0.61
Mean tidal volume (n=139)	486 (435, 552)	400 (375, 424)	0.14
Max FiO2	99 (97.4, 100)	99 (98, 99.5)	0.91
Mean FiO2	50.8 (35.5, 63.4)	54.2 (51.8, 62.8)	0.47
Max PEEP (n=112)	6 (5, 9)	4.5 (4, 5)	0.36
Mean PEEP (n=112)	5 (5, 6)	4.5 (4, 5)	0.29

Characteristic	Non-ARDS (n=309)	ARDS (n=7)	<i>P</i> value
Max PIP (n=139)	30 (25, 34)	35 (28, 42)	0.40
Mean PIP (n=139)	19.6 (17.1, 23.2)	26.8 (19.6, 34)	0.06

Continuous data expressed as median (25–75% interquartile range). Categorical variables expressed as a percentage of available data. $P < 0.05$ was considered statistically significant.

ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; COPD: chronic obstructive lung disease; GERD: gastroesophageal reflux disease; EBL: estimated blood loss; FiO₂: fraction of inspired oxygen; fluid balance: (crystalloid+colloid)÷(EBL+urine output); ILD: interstitial lung disease; PEEP: positive end expiratory pressure; PIP: peak inspiratory pressure ; PPI: proton pump inhibitors.

¹For months from last bleomycin dose, because one PO-ARDS case occurred after the 6th surgery, a repeat analysis was performed which excluded this case. From this analysis the median time (IQR) was 6.4 (2.2, 201.3) months which was not significantly different from the Non-ARDS controls ($p = 0.16$).

Table 3

Secondary outcomes of non-ARDS and ARDS patients (all procedures)

Characteristic	Non-ARDS (n=309)	ARDS (n=7)	<i>P</i> value
Hospital LOS	9.2 (5.7, 13.2)	26.1 (12, 65.8)	<0.001
Invasive ventilator days	0.52 (0.32, 0.78)	3.2 (2.1, 20.2)	<0.001
PO-ICU Admission	67 (21.6%)	6 (85.7%)	<0.001
ICU free days	26.4 (24.3, 27.1)	21.3 (11.7, 25.2)	0.03
Death during hospitalization	8 (2.6%)	1 (14.3%)	0.18

Continuous data expressed as median (25–75% interquartile range). Categorical variables expressed as a raw number and percentage of available data.