Preoperative and Intraoperative Predictors of Postoperative Acute Respiratory Distress Syndrome in a General Surgical Population

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CME This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: Acute respiratory distress syndrome (ARDS) is a devastating condition with an estimated mortality exceeding 30%. There are data suggesting risk factors for ARDS development in high-risk populations, but few data are available in lower incidence populations. Using risk-matched analysis and a combination of clinical and research data sets, we determined the incidence and risk factors for the development of ARDS in this general surgical population.

Methods: We conducted a review of common adult surgical procedures completed between June 1, 2004 and May 31, 2009 using an anesthesia information system. This data set was merged with an ARDS registry and an institutional death registry. Preoperative variables were subjected to multivariate analysis. Matching and multivariate regression was used to determine intraoperative factors associated with ARDS development.

Results: In total, 50,367 separate patient admissions were identified, and 93 (0.2%) of these patients developed ARDS. Preoperative risk factors for ARDS development included American Society of Anesthesiologist status 3–5 (odds ratio [OR] 18.96), emergent surgery (OR 9.34), renal failure (OR 2.19), chronic obstructive pulmonary disease (OR 2.16), number of anesthetics during the admission (OR 1.37), and male sex (OR 1.65). After matching, intraoperative risk factors included drive pressure (OR 1.17), fraction inspired oxygen (OR 1.02), crystalloid administration in liters (1.43), and erythrocyte transfusion (OR 5.36).

What We Already Know about This Topic

- Postoperative adult respiratory distress syndrome (ARDS) develops after high-risk surgical cases

What This Article Tells Us That Is New

- Of 50,367 hospitalizations, 93 (0.2%) were complicated by postoperative ARDS with a median time to onset of 2 days
- There were several significant differences between the patients who did and did not develop ARDS; American Society of Anesthesiologists 1-2 patients had an extremely low risk of developing ARDS

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of Anesthesiology, page 9A.

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Conclusions: ARDS is a rare condition postoperatively in the general surgical population and is exceptionally uncommon in low American Society of Anesthesiologists status patients undergoing scheduled surgery. Analysis after matching suggests that ARDS development is associated with median drive pressure, fraction inspired oxygen, crystalloid volume, and transfusion.

ACUTE respiratory distress syndrome (ARDS) is a clinical syndrome that is defined as the rapid onset of hypoxia with a Pa_{O_2}/fraction inspired oxygen (F_{IO_2}) (P/F) ratio ≤300 and bilateral pulmonary infiltrates in the absence of left atrial hypertension.[1] The overall in-hospital mortality of patients with ARDS is commonly thought to exceed 30%.[2,3] A subset of patients undergoing operative procedures is at higher risk for postoperative ARDS. Cardiac, thoracic, vascular, and trauma surgeries are high risk for the development of postoperative ARDS[4–7]; however, the incidence and risk factors for new-onset postoperative ARDS in the noncardiothoracic, vascular, and trauma surgical populations have not been well defined. In addition, intraoperative ventilator and fluid management may influence the incidence of ARDS after pneumonectomy and other intrathoracic procedures.[7,8] Hence, ventilator and fluid management may impact ARDS development in other populations.[9]

In our previous work, we demonstrated that patients with a low intraoperative P/F ratio were typically managed using increased F_{IO_2} and peak airway pressures.[10] We have also shown that patients with a preoperative diagnosis of ARDS are not typically managed using a lung protective ventilation strategy incorporating low tidal volumes (Vt) and levels of positive end-expiratory pressure (PEEP) supported by the critical care literature.[11] However, this previous work did not explicitly investigate patients without ARDS before their operation. Therefore, we sought to determine the incidence of new-onset ARDS in what have traditionally been thought of as low-incidence cases in a broad surgical population. Furthermore, we sought to determine preoperative risk factors for the development of ARDS in this population, and whether intraoperative management of patients who developed ARDS was fundamentally different from those patients who did not develop the condition. We tested the hypothesis that patients with known predictors of end-organ dysfunction, large volume resuscitations, and extended exposure to elevated ventilator settings would be at increased risk for the development of postoperative ARDS.

Materials and Methods

Institutional Review Board approval was obtained for this cohort study at The University of Michigan Health System (IRB-MED, Ann Arbor, Michigan), a large, quaternary care facility. All data were deidentified before analysis, and a waiver of consent was obtained for this study. All cases recorded in the anesthesia information management system (Centricity, General Electric Healthcare, Waukesha, WI) from June 1, 2004 through May 31, 2004 were screened for inclusion. All cases on the cardiac, thoracic, transplant, trauma, and vascular surgery services were excluded, as were cases with no recorded service.

Preoperative data were prospectively collected from routine clinical documentation that was entered into the anesthesia information management system at the point of care. The record includes a structured preoperative history and physical examination, allowing for coded entry and free text where required. Data abstracted from the preoperative history included age, sex, primary surgical service, American Society of Anesthesiologists (ASA) classification, diabetes, hypertension, coronary artery disease, congestive heart failure, renal failure, liver disease, asthma, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, smoking status, and height. Variables were selected for either their previous association with the development of ARDS, necessary for the management of patients with ARDS, or confer a high risk of organ dysfunction potentially requiring intensive care unit admission.[5,6,12–15] Variables that may be associated with the development of ARDS but do not have a structured area of documentation in the anesthesia information management system were not included in the analysis. A detailed description of variable definitions is included in the appendix. Free-text entries were hand-coded by the research team for analysis. From the height variable, the predicted body weight was calculated for this study using the formula 50 + 2.3 (height [in] – 60) for men and 45.5 + 2.3 (height [in] – 60) for women.

Unique hospital admissions were considered as the base unit for analysis. In those admissions containing multiple anesthetic cases, data were analyzed from the last case of the admission or the last case before development of ARDS, as appropriate. Records from the final anesthetic of each admission were also used to determine preoperative comorbidities and ASA status. For those hospitalizations containing multiple surgical cases, the total number of surgical procedures during each admission was also calculated and included in analysis. After initial analysis, it was decided that multiple admissions in the 7 days before an ARDS event would be managed by retaining the admission most proximal to the diagnosis and excluding the other admissions.

Intraoperative physiologic and ventilator data were acquired using an automated, validated electronic interface from the anesthesia machine (Aisys; General Electric Healthcare) and physiologic monitors (Solar 9500; General Electric Healthcare).[12,13,16,17] F_{IO_2}, peak inspiratory pressure (PIP), exhaled Vt, PEEP, oxyhemoglobin saturation, drive pressure (ΔP, defined as PIP – PEEP), and respiratory rate were obtained and analyzed for median values to eliminate spurious and isolated values. Based on previous data, the duration of high-pressure ventilation may be associated with development of ARDS.[7] Considering these data, we chose to examine the number of 10-min epochs of median PIP >30 cm H_2O and number of 10-min epochs of median Vt >12 cc/kg predicted body weight from the time of incision to the end of

anesthesia.[2] This technique has been used in previous studies to eliminate artifact and spurious values over relatively short periods of time.[12,13]

Case times were validated as having started and ended by having electronically documented heart rate from electrocardiogram or electronically documented start, incision, and end times in the event electrocardiogram data were not available. Cases with negative or undocumented times were excluded. Cases from patients graded as ASA classification 6 were also excluded because the ventilation strategy implemented may have been designed to favor perfusion to other organs. A summary of inclusion and exclusion criteria are presented in figure 1.

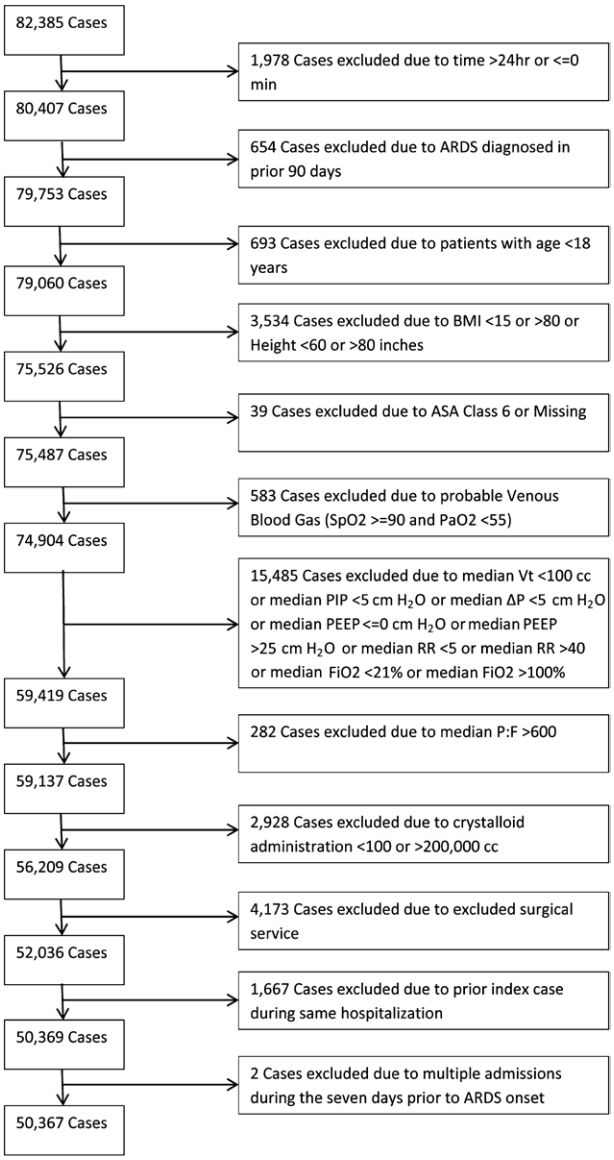

Fig. 1. Method of case exclusion: * Ventilator setting exclusion criteria include Vt < 100 cc, PIP < 5 cm H_2O, driving pressure < 5 cm H_2O, 0 > PEEP > 25 cm H_2O, 5 > RR > 40, 0.21 cc > FIO_2 > 10. ** Other exclusion criteria for which no additional patients were excluded were 45 mmHg > PaO_2 > 600 mmHg, PIP epochs < 0, Vt Epochs < 0, PRBC > 200 units, FFP > 200 units, Colloid < 0 units, Cryoprecipitate < 0 units. ARDS = acute respiratory distress syndrome; ASA = American Society of Anesthesiologists; BMI = body mass index; FFP = fresh frozen plasma; PaO_2 = partial pressure of oxygen; P:F = PaO_2/FIO_2; PRBC = packed erythrocytes; SpO_2 = hemoglobin saturation; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; RR = respiratory rate; Vt = tidal volume.

When available, we analyzed values for the intraoperative arterial blood gases that were manually entered by the anesthetic team into the structured electronic perioperative information system (Centricity; General Electric Healthcare). From the recorded intraoperative PaO_2 values and FIO_2, the P/F ratio was calculated for each available blood gas. Volumes of crystalloid, colloid, units of packed erythrocytes, units of fresh frozen plasma, and units of platelets were also obtained from the electronic anesthetic record.

To identify the subpopulation of patients who went on to develop ARDS, patients in the operative data set were merged with a dedicated prospectively collected research data set of all adult critical care patients on ventilators at the University of Michigan Medical Center who were screened for entry into ARDS studies. For the purposes of this investigation, only patients receiving mechanical ventilation after their anesthetic were screened for ARDS. In this research data set, ARDS was diagnosed through analysis of the patient's ventilator status, arterial blood gases, chest x-ray, and clinical documentation. Patients were deemed positive for the primary outcome of ARDS if they were on a ventilator, had bilateral infiltrates on chest x-ray as determined by a clinician, had a P/F ratio ≤300, and had minimal evidence of left atrial fluid overload. Patients were included in the postoperative ARDS group if the date of ARDS onset was determined to be between postoperative days 0 and 7, inclusive. Patients who developed ARDS on the day of their operation were examined by one of the authors (Dr. Blum), and those with a diagnosis of ARDS before their anesthetic were excluded. Finally, mortality data were collected from an institutional death database to compare the mortality of the propensity-matched groups both with and without ARDS to determine the risk presented to patients who develop ARDS. This database is constructed using multiple resources, including in-hospital mortality, failed follow-up at clinic visits, and the social security death master file.

Statistical Analysis

Statistical analysis was performed using R version 2.14 (R Foundation for Statistical Computing, Vienna, Austria). Population characteristics were examined using the Student *t*-test, Pearson chi-square test, Mann–Whitney U test, or Fisher exact test, as appropriate for the distribution of the data. Collinearity diagnostics were performed, and a condition index greater than 30 was examined with a bivariate correlation matrix, with a pairwise correlation threshold of greater than 0.70 for problematic collinearity. All variables that were significantly different between groups

($P < 0.05$) were entered into a logistic regression model. Bootstrap samples ($R = 1{,}000$ replicates) were chosen, and backward stepwise selection was used to fit a parsimonious regression model to each sample. It was determined *a priori* that those variables retained in ≥60% of all bootstrapped models would be retained for the final model.[18] This parsimonious model was fit in $R = 1{,}000$ bootstrap samples to determine percentile CI for the odds ratio (OR) and absolute risk difference for each variable.[19,20] The fit and predictive capability of the model was assessed using 10-fold cross-validation of the Hosmer–Lemeshow goodness-of-fit test and receiver operating characteristic-area under the curve (ROC-AUC).[21]

Controls were then matched to cases based on their preoperative likelihood of developing ARDS. All preoperative variables that were significantly different between groups were entered into an optimal matching algorithm, which is similar to a greedy algorithm but also minimizes the overall distance between groups.[22,23] The data analysis plan specified that all cases of ARDS were to be retained if the intravariable difference between matched groups was reduced to less than 0.2 SD. In the case of intravariable differences greater than 0.2 SD, data would first be grouped into appropriate quantiles for those variables, and then matching would proceed within each quantile. After initial data analysis, the matching ratio was increased to 4:1, which would be sufficient to detect a between-group difference in ΔP of 2 cm H_2O or Vt of 0.75 cc/kg with >80% power. Percent improvement in balance between the groups was examined, and population characteristics were again described using the appropriate statistical tests.

The role of intraoperative management was then examined through a second predictive model, constructed on the risk-matched patient population. Median ΔP, median respiratory rate, median F_{IO_2}, number of 10-min epochs of PIP ≥30 cm H_2O, number of 10-min epochs of Vt ≥12 cc/kg predicted body weight, transfusion of packed erythrocytes, transfusion of platelets, use of fresh frozen plasma, use of colloid, total volume of crystalloid, and duration of case were entered into a conditional logistic regression model, accounting for the matched nature of the data. Backward stepwise conditional logistic regression was used within bootstrap samples ($R = 1{,}000$), as described above. Those variables that were significant predictors in ≥60% of samples comprised the final parsimonious predictive model. Bootstrap percentile CIs were constructed for the ORs of each predictor. This model was examined using the Hosmer–Lemeshow goodness-of-fit statistic and the ROC-AUC. Calculation of absolute risk difference and cross-validation of the ROC-AUC were not performed, as conditional logistic regression models cannot be used for computing the predicted values necessary for these statistics.[18,19,24]

Due to the hierarchical nature of the study design, some patients contributed multiple cases to the data set. Intraclass correlation coefficients were estimated for each variable to understand the degree to which repeated measures were likely to be correlated with previous measures. To quantify the effect of these correlations on the predictive models, a sensitivity analysis was performed in a data set without multiple observations. Specifically, only those patients who had a single anesthetic during their first admission were included; any further admissions for those patients were excluded from the data set. The analysis above was repeated with only these patients.

Furthermore, because a considerable number of cases did not have a recorded estimated blood loss (EBL), this variable was excluded from the initial model and considered in a separate sensitivity analysis. Cases were divided into EBL quintiles and then matched within each quintile based on preoperative risk factors, as above. After thus controlling for surgical blood loss, the intraoperative parsimonious predictive model developed above was fit to these data and bootstrap percentile CI determined for the OR and absolute risk difference of each predictor.

Results

Data were reviewed for 82,385 anesthetic cases, and a summary of excluded cases is shown in figure 1. Of the 50,367 hospitalizations analyzed, 93 (0.2%) were complicated by postoperative ARDS. The median time to onset of postoperative ARDS was 2 days (fig. 2). There were several significant differences in patients who did and did not develop postoperative ARDS (table 1). Most patients were admitted only once during the study period (34,535 patients, 83.8%), although the number of admissions per patient ranged from 1 to 15 (table 2). The majority of hospitalizations contained only one anesthetic case during that admission (48,873 admissions, 97.0%), although the number of cases per admission ranged from 1 to 14 (table 2).

In an attempt to reduce the impact of linked factors in the regression, a condition number of 13.8 was calculated, well below the threshold of 30, suggesting that no changes

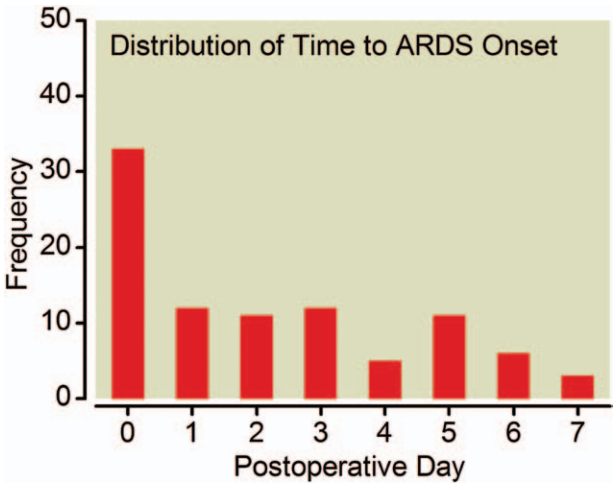

Fig. 2. Postoperative day of ARDS onset. ARDS = acute respiratory distress syndrome.

Table 1. Patient Characteristics

	ARDS (n = 93)		Control (n = 50,274)		
	Median	IQR	Median	IQR	*P* Value
Age	59	(48.0, 73.0)	51	(39.0, 63.0)	<0.001
BMI	26.9	(22.8, 34.8)	27.6	(24.0, 32.4)	0.996
Anesthetics per admission	1	(1, 1)	1	(1, 1)	<0.001
	n	%	n	%	
Male	62	67	23,210	46	<0.001
Emergent case	33	35	2,145	4	<0.001
ASA class ≥ 3	86	92	15,759	31	<0.001
Former smoker	20	22	10,132	20	0.700
Current smoker	18	19	8,242	16	0.403
Ethanol abuse	6	6	1,667	3	0.133
Diabetes	25	27	6,558	13	<0.001
Hypertension	50	54	18,204	36	0.001
Coronary artery disease	17	18	4,032	8	0.002
Congestive heart failure	12	13	1,534	3	<0.001
Renal failure	25	27	2,729	5	<0.001
Liver disease	3	3	954	2	0.260
Asthma	1	1	3,987	8	0.007
COPD	22	24	2,694	5	<0.001
Sleep apnea	10	11	4,378	9	0.460

ARDS = acute respiratory distress syndrome; ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; IQR = interquartile range.

Table 2. Summary of Anesthetic Frequencies per Admission and Number of Admissions per Patient

No. of Anesthetics	No. of Admissions in Data Set (n, %)	%	No. of Admissions	No. of Patients	%
1	48,873	97.0	1	34,535	83.8
2	1,118	2.2	2	5,008	12.2
3	228	0.5	3	1,121	2.7
4	79	0.2	4	341	0.8
5	33	0.1	5	106	0.3
6–10	30	0.1	6–10	72	0.2
11–14	6	0.0	11–15	6	0.0

were necessary to address collinearity. Seven variables were retained in ≥60% of bootstrap samples: ASA physical status ≥3, emergent procedure, asthma, renal failure, COPD, male gender, and the number of anesthetics during admission (table 3). In 10-fold cross-validation, the Hosmer–Lemeshow goodness-of-fit test was nonsignificant in each validation sample, and the mean ROC-AUC was 0.886 (95% CI: 0.785–0.979).

Matching resulted in a 99.2% balance improvement, and all intravariable differences between matched groups were less than 0.2 SD. No significant differences remained between the two matched groups after matching (table 4). After matching on preoperative risk, mortality remained significantly higher in the group that developed ARDS than in the control group, both at 28 days (22% *vs.* 7%, $P < 0.001$) and at 90 days (27% *vs.* 12%, $P < 0.001$).

To assess the impact of intraoperative management on subsequent ARDS development, a predictive model was built, including several ventilator and transfusion settings. A summary of variables examined is provided in table 5. Five variables were retained in ≥60% of reverse selection bootstrap replicates: median ΔP, median F_{IO_2}, transfusion of packed erythrocytes, transfusion of platelets, and total volume of crystalloid administered (table 6). This model was well fit by the Hosmer–Lemeshow test ($P = 0.718$). The ROC-AUC for this model was 0.851 (DeLong 95% CI: 0.805–0.897).

By identifying those patients who underwent only a single anesthetic during their first admission and excluding any further admissions for those patients, we constructed a cohort of 37,697 unique patients, of whom 62 (0.16%) developed postoperative ARDS. Analysis of this cohort

Table 3. Preoperative Predictors of ARDS with Associated Absolute Risk Reduction and Odds Ratio

	No. of Models Retaining Variable	OR	Absolute Risk Difference	Significant at $\alpha = 0.05$
ASA ≥ 3	1,000	18.96 (9.63, 61.39)	0.40% (0.30, 0.50)	*
Emergent procedure	1,000	9.34 (5.69, 14.52)	1.00% (0.61, 1.40)	*
Asthma	969	0.13 (0.00, 0.52)	–0.17% (–0.23, –0.09)	
Renal Failure	936	2.19 (1.28, 3.39)	0.18% (0.04, 0.33)	*
COPD	907	2.16 (1.24, 3.54)	0.18% (0.04, 0.36)	*
Male	837	1.65 (1.04, 2.55)	0.09% (0.01, 0.16)	*
No. of anesthetics during admission	797	1.37 (1.10, 1.61)	0.05% (0.02, 0.07)	*
CAD	471	—	—	
Hypertension	356	—	—	
CHF	245	—	—	
Age	223	—	—	
Diabetes	175	—	—	

ASA = American Society of Anesthesiologists; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; OR = odds ratio.

found preoperative predictors identical to those selected in the larger population, with very similar OR, except for the logical removal of the number of cases per admission. Intraoperative predictors for this cohort were also quite similar, although only median ΔP (OR 1.15, 95% CI: 1.05–1.31), packed erythrocyte transfusion (OR 4.05, 95% CI: 1.29–17.55), and volume of crystalloid in liters (OR 1.56, 95% CI: 1.13–2.29) achieved statistical significance.

Valid estimates of surgical blood loss (EBL) were available for 30,234 cases, of which 71 (0.23%) resulted in postoperative ARDS. Within each EBL quintile, cases were matched to controls based on preoperative risk factors. After controlling for EBL, median ΔP (OR 1.17, 95% CI: 1.09–1.27), platelet transfusion (OR 13.59, 95% CI: 1.09–100), and volume of crystalloid in liters (OR 1.43, 95% CI: 1.02–2.26) remained significant risk factors for ARDS development.

Discussion

ARDS is among the most devastating postoperative complications and is associated with significant mortality.[5,25] The main results of this study are as follows: (1) In a general surgical population presenting to the operating room without ARDS, the overall incidence of new-onset postoperative ARDS was approximately 0.2%; (2) The risk of ARDS was extremely low in ASA class 1–2 patients; (3) Patients with ASA classes 3–5, emergency surgery, renal failure, COPD, and multiple anesthetics are at an increased risk of ARDS; (4) After controlling for patient comorbidities and risk factors, intraoperative ΔP, increased F_{IO_2}, volume of crystalloid, and transfusion are associated with the development of ARDS; and (5) Development of ARDS greatly increases patient mortality, regardless of preoperative comorbidities.

Considerable research has helped ascertain preoperative risk factors for postoperative respiratory complications.[26–30] Although there is some literature investigating the development of ARDS postoperatively, most of this work has focused on high-risk elective surgeries, such as cardiac and thoracic interventions.[3–7,31] This study focused on a relatively common surgical population, a group of patients seen in hospitals throughout the world with a low incidence of ARDS that has precluded prospective study.

Preoperative univariate associations with the development of ARDS in our cohort were similar to previous studies, reflecting a greater number of comorbidities among the patients who developed ARDS.[5,7] In multivariate analysis, only ASA status, emergent surgical procedure, renal failure, COPD, and number of anesthetics were significant predictors of future ARDS. A history of being an active smoker and ethanol abuser did not meet statistical significance for predicting ARDS, although they have been associated with ARDS risk in other populations.[7] This may be because such conditions are common in the surgical populations which prior studies have focused upon. The great importance of ASA status in predicting postoperative ARDS suggests that the actual comorbidities are less important, except for renal failure and COPD, than the preoperative medical optimization of comorbidities. From

Table 4. Patient Characteristics after Matching on Preoperative Risk of ARDS

	ARDS (n = 93)		Control (n = 372)		
	Median	IQR	Median	IQR	*P* Value
Age	59	(48, 73)	59	(47, 70)	0.651
Anesthetics per admission	1	(1, 1)	1	(1, 1)	0.382
	n	%	n	%	
Male	62	67	233	63	0.547
Emergent case	33	35	129	35	0.903
ASA					0.351
1	0	0	11	3	—
2	7	8	18	5	—
3	48	52	179	48	—
4	37	40	160	43	—
5	1	1	4	1	—
Former smoker	20	22	113	30	0.097
Current smoker	18	19	61	16	0.537
Ethanol abuse	6	6	23	6	1.000
Diabetes	25	27	100	27	1.000
Hypertension	50	54	184	49	0.488
Coronary artery disease	17	18	63	17	0.760
Congestive heart failure	12	13	51	14	1.000
Renal failure	25	27	94	25	0.791
Liver disease	3	3	12	3	1.000
Asthma	1	1	11	3	0.474
COPD	22	24	77	21	0.571

ARDS = acute respiratory distress syndrome; ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; IQR = interquartile range.

Table 5. Intraoperative Characteristics after Matching on Preoperative Risk of ARDS

	ARDS (n = 93)		Control (n = 372)		
	Median	IQR	Median	IQR	*P* Value
Median Δ Pressure	24	(19, 28)	18	(15, 22)	<0.001
Median PIP	27	(22, 33)	21	(17, 26)	<0.001
Median PEEP	4	(2, 5)	4	(0, 5)	0.233
Median tidal volume	580	(479, 690)	553	(480, 616)	0.003
Median tidal volume (cc/kg PBW)	9.0	(7.5, 10.1)	8.5	(7.3, 9.7)	0.053
Epochs of PIP ≥30	1	(0, 14)	0	(0, 0)	<0.001
Epochs of Vt >12 cc/kg PBW	0	(0, 1)	0	(0, 0)	<0.001
Median RR	12	(10, 14)	11	(10, 12)	0.02
Median F_{IO_2}	76	(52, 96)	55	(45, 93)	0.001
Case length, min	251	(189, 410)	180	(120, 268)	<0.001
Crystalloid (liters)	3.2	(2.0, 4.8)	2.0	(1.3, 3.0)	<0.001
	n	%	n	%	
Received packed erythrocytes	38	41	54	15	<0.001
Received platelets	13	14	15	4	0.001
Received colloid	37	40	67	18	<0.001
Received FFP	13	14	17	5	0.003

ARDS = acute respiratory distress syndrome; F_{IO_2} = fraction of inspired oxygen; FFP = fresh frozen plasma; IQR = interquartile range; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; RR = respiratory rate; Vt = tidal volume.

Table 6. Intraoperative Predictors of ARDS after Matching on Preoperative Risk of ARDS

	Bootstraps Retaining Variable (No.)	OR	Significant at $\alpha = 0.05$
Median drive pressure	914	1.17 (1.09, 1.31)	*
Packed erythrocyte transfusion	869	5.36 (1.39, 11.11)	*
Median FIO_2	797	1.02 (1.00, 1.05)	*
Crystalloid (liters)	704	1.43 (1.15, 1.93)	*
Platelet transfusion	621	5.36 (0.88, 64.75)	
Epochs of PIP ≥30	511	—	
Median RR	424	—	
Case duration	361	—	
Median Vt	335	—	
Colloid administration	303	—	
FFP transfusion	282	—	
Epochs of Vt ≥12 cc/kg	249	—	

*Variable is significant after bootstrapping.

FIO_2 = fraction of inspired oxygen; FFP = fresh frozen plasma; OR = odds ratio; PIP = peak inflation pressure; RR = risk ratio; Vt = low tidal volume.

these data, ASA 1 and 2 patients are at low risk for the development of ARDS, and patients undergoing emergency surgery may present a unique cohort deserving special attention.

The data from this study suggest that asthmatic patients may be protected from ARDS. Although a type I error is possible given the low incidence of asthma in our population, several asthma treatments have been suggested to be potentially effective in ARDS, despite sparse data.[32–36] Previous studies have focused on the administration of agents after the onset of ARDS, whereas the patients in our study would have received treatment prophylactically. Although beyond the scope of the present investigation, this is an issue that we feel is worthy of future study.

After matching, it seems that intraoperative ventilator management may impact the development of postoperative ARDS. The finding that exposure to higher ΔP seems to increase the odds of ARDS development is consistent with the findings by other investigators in higher risk populations demonstrating that increased PIPs were similarly predictive of ARDS.[5,7] However, our data suggest that exposure to elevated PIP with a lack of PEEP is a component of the development of ARDS. This may be because such ventilator settings introduce barotrauma and atelectrauma, potentially compounding lung injury. The fact that increased pressures but not increased Vt were predictive of future ARDS is interesting. Much of the work in the critical care community in preventing ARDS mortality has focused on the use of low Vt ventilation.[2,37–41] Previous perioperative literature suggests that both pressure and volume may be important in preventing ARDS. Increased pressures seem to be consistent predictors of future ARDS,[4–7,31] while a protocol that focused on low Vt and, consequently, lower plateau pressures has shown a specific association with a reduction in the incidence of ARDS in thoracic surgery patients.[8] Our current study seems to support that increased ΔP with low PEEP is associated with the development of ARDS to a greater degree than elevated Vt or PIP alone.

Our analysis also showed intraoperative fluid and transfusion of blood products to be significantly associated with the onset of ARDS. Transfusion-related acute lung injury has been described in the literature.[42] The use of blood products in our population may be an indicator of more aggressive resuscitation, and as such, this would support works that showed that increased volume resuscitation was predictive of future ARDS.[5,8,9,43] Given the observational nature of the current study, no recommendations can be made about the use of blood products or volume resuscitation intraoperatively for the prevention of ARDS, but this area certainly warrants further investigation.

ARDS is known to be associated with approximately 30–40% mortality at 90 days.[2,25,44] In our previous work, patients who underwent an anesthetic at our institution with a preoperative diagnosis of ARDS had a 90-day mortality of 32% compared to 19% mortality for those who underwent an anesthetic with a P/F ratio <300 without meeting criteria for ARDS.[11] Fernandez-Perez found a 60-day mortality of 27% compared to 1% for patients who did not have pulmonary complications.[5] In this study, after matching, we have shown 27% mortality at 90 days for those patients who develop ARDS after their anesthetics compared to 12% for those who do not. The development of ARDS in this cohort is associated with an increase in mortality and is a worthwhile target for efforts at prevention.

This study has several limitations. First, the data were collected as part of routine clinical care and were not subject to the validation processes used in prospective trials. Although data are typically entered through a predefined selection process for each variable, there was no formal training on the definitions for each variable (appendix). In addition, free text is allowed in all fields and was subject to interpretation by the research team. Models from such data have become common in the literature and have correlated with models based on prospectively collected data by dedicated research staff.[13,45] In addition, items that may be associated with the development of ARDS that are not provided with specific coded entry boxes, such as sepsis and aspiration, were not included in the model. Next, the data are from a single, large, quaternary care center, collected over several years. The patient population may have changed over time and may not represent the typical patient seen in other locations. The database used to determine whether patients had ARDS required mechanical ventilation and hence may underestimate the true frequency of ARDS. The etiology of the ARDS, whether it was primary or secondary to another insult, was not determined and may itself be predictive of outcome. In addition, we cannot be completely confident the elevated ΔP and increased F_{IO_2} requirements were not signs of ARDS that had developed since the last datapoint was obtained preoperatively. Intraoperatively, there was no collection of plateau pressures, and hence analysis was limited to PIP. Although PIP has been used in several intraoperative ARDS manuscripts, it is limited and can be considerably higher than plateau pressures based on a variety of factors. Finally, the mortality data are based on an internal death registry and may not capture potential mortality of patients who were discharged to another long-term facility for ongoing care.

Due to the observational nature of this study, we did not have specific protocols for the intraoperative and postoperative management of the patient population other than routine clinical care. There was no mandated ventilator or fluid protocol at any point during the care of the patients involved in this study, including the postoperative period. However, despite this, there were statistically significant predictors of future ARDS determined both preoperatively and intraoperatively. Furthermore, in observational studies using clinical databases, the problem of model overfitting can be particularly vexing. We used several different bootstrapping techniques to reduce the variance in our models and select robust predictors, thereby minimizing the risk of type I statistical error. However, no amount of statistical testing can replace prospective validation of the predictive model and further study of interventions to mitigate risk. Ideally, the best evidence supporting the role of high-pressure ventilation and development of ARDS in the surgical population would be a randomized controlled trial. Using the preoperative predictors described, one could develop criteria for enrollment in such a trial. However, careful consideration must be given to the design and ethical implications of such a study.

Despite the limitations, this investigation provides new evidence for a poorly studied population. We again demonstrated the high attributable mortality associated with the diagnosis of postoperative ARDS. We documented an exceptionally low incidence of postoperative ARDS in a general surgical population, particularly in the ASA 1 and 2 patients. Postoperative ARDS was predicted with high reliability using a model based on preoperative ASA status, emergent surgical case, COPD, renal failure, and multiple surgeries. After matching, additional intraoperative risk factors for the development of ARDS (ΔP, increased F_{IO_2}, fluid administration, and transfusion) were identified, potentially offering clinicians opportunities to reduce the risk of postoperative ARDS. However, further investigation is still required before causation can be firmly established.

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Appendix: Anesthesia Information Management System Fields

Below are the fields available in the Centricity Anesthesia Information Management System that were coded as positive for each comorbidity examined. Fields that contained provider-entered free text were reviewed and hand-coded by the research team. Common free-text entries are also provided for relevant fields; while these are not exhaustive, they are representative of the data considered to indicate a positive response for each condition.

Hypertension: Duration: <Any>
Hypertension: Control: <Any>
Hypertension: Reported Usual BP: Any
- Common text responses coded as positive:
  - "Borderline"
  - "Treated with diet/exercise"

Diabetes: Type: <Any>
Diabetes: Treatment: <Any>
Diabetes: Onset: <Any>
- Common text responses coded as positive:
  - "Prediabetes"
  - "Insulin resistance"
  - "Glucose intolerance"
  - "Gestational diabetes"

CAD: Class: <Any>
CAD: Treatment: <Any>
CAD: CABG
CAD: Angioplasty
CAD: "CAD recorded, no symptoms"
CAD: Stability: <Any>
- Common text responses coded as positive:
  - "CABG"
  - "Coronary stent(s)"
  - "History of MI (myocardial infarction)"

CHF: Chronicity: <Any>
CHF: Class: <Any>
CHF: Etiology: <Any>
Renal Failure: Type: <Any>
Renal Failure: Etiology: <Any>
Renal Failure: Chronic insufficiency
Renal Failure: Complications: <Any>
Renal Failure: CRI
Renal Failure: Cr <Any>
Renal Failure: Last Dialyzed: <Any>
- Common text responses coded as positive:
  - "S/P Renal transplant"

Liver Disease: Hepatitis Type: <Any>
Liver Disease: Ascites
Liver Disease: Cirrhosis
- Common text responses coded as positive:
  - "Autoimmune hepatitis"
  - "Wilson Disease"
  - "Steatohepatitis"

Asthma: Classification: <Any>
Asthma: Symptom Frequency: <Any>
Asthma: ER Visits: <Any>
Asthma: Hospitalization: <Any>
COPD: Type: <Any>
COPD: Severity: <Any>
Sleep Apnea: "Treated by BIPAP/CPAP"
Sleep Apnea: "Snores loud enough to wake themselves/others up"
Sleep Apnea: "Symptomatic, untreated"
Sleep Apnea: "Stops breathing at night"
Sleep Apnea: "Tested positive for sleep apnea"
Sleep Apnea: "Treated by surgery"
Alcohol: Abuse History: Current abuser
Alcohol: Drinks Per Day: <Any number greater or equal to two>
Alcohol: Amount: High

BIPAP = bilevel positive airway pressure; BP = blood pressure; CAD = coronary artery disease; CABG = coronary artery bypass graft; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; Cr = Creatinine; CRI = chronic renal insufficiency; ER = emergency room; MI = myocardial infarction; S/P = status post.