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# Risk Factors Associated With Early Postoperative Respiratory Failure: A Matched Case-Control Study

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ABSTRACT

*Background:* Postoperative respiratory failure is the most common serious postoperative pulmonary complication, yet little is known about factors that can reduce its incidence. We sought to elucidate modifiable factors associated with respiratory failure that developed within the first 5 d after an elective operation.

*Materials and Methods:* Matched case-control study of adults who had an operation at five academic medical centers between October 1, 2012 and September 30, 2015. Cases were identified using administrative data and confirmed via chart review by critical care clinicians. Controls were matched 1:1 to cases based on hospital, age, and surgical procedure.

*Results:* Our total sample ($n = 638$) was 56.4% female, 71.3% white, and had a median age of 62 y (interquartile range 51, 70). Factors associated with early postoperative respiratory failure included male gender (odds ratio [OR] 1.72, 95% confidence interval [CI] 1.12-2.63), American Society of Anesthesiologists class III or greater (OR 2.85, 95% CI 1.74-4.66), greater number of preexisting comorbidities (OR 1.14, 95% CI 1.004-1.30), increased operative duration (OR 1.14, 95% CI 1.06-1.22), increased intraoperative positive end-expiratory

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pressure (OR 1.23, 95% CI 1.13-1.35) and tidal volume (OR 1.13, 95% CI 1.004-1.27), and greater net fluid balance at 24 h (OR 1.17, 95% CI 1.07-1.28).
*Conclusions:* We found greater intraoperative ventilator volume and pressure and 24-h fluid balance to be potentially modifiable factors associated with developing early postoperative respiratory failure. Further studies are warranted to independently verify these risk factors, explore their role in development of early postoperative respiratory failure, and potentially evaluate targeted interventions.



## Introduction

Postoperative respiratory failure (PRF)—defined as unplanned reintubation, prolonged mechanical ventilation, or inadequate oxygenation or ventilation—is the most common serious postoperative pulmonary complication, with an incidence of up to 7.5%.[1-11] Cases of PRF have been associated with an excess of $53,000 in hospital charges, 9 extra days of hospitalization, and a 22% increase in in-hospital mortality, after adjusting for known preoperative risk factors.[12-16] Operations complicated by postoperative respiratory failure had 3.74 times higher adjusted odds of death than those not complicated by respiratory failure, 1.47 times higher odds of 90-day readmission, and 1.86 times higher odds of an outpatient visit with one of 44 postoperative conditions (e.g., bacterial infection, fluid and electrolyte disorder, abdominal hernia) within 90 d of hospital discharge.[14,17]

While clinicians intuitively understand the severity of PRF and some of the factors that likely contribute to its occurrence (e.g., over-sedation and fluid overload), progress in reducing the incidence of PRF (considered broadly across all procedure types) has been stymied by a lack of consensus regarding which patients are most at risk, which causative pathways and phenotypic presentations are most relevant, and which potentially modifiable risk factors are most important. Although it can seem obvious to clinicians why PRF occurred in a particular case, few if any studies have identified systematic interventions to prevent it. Additional information about PRF in a broadly representative group of postoperative patients is necessary to bridge the gap between clinicians' intuitive understanding and potential interventions.

We sought to evaluate patient- and procedure-related risk factors associated with development of PRF following elective surgical procedures in adult patients. We were especially interested in identifying potentially modifiable or optimizable patient comorbidities and determining if intraoperative fluid, ventilator, and medication management were associated with early PRF. We hypothesized that patients with more (or more severe) preexisting comorbidities, higher intraoperative ventilator volume and/or pressure settings, higher net positive fluid balance at 24 h, and increased intraoperative analgesia and sedative doses would have increased odds of developing PRF.

## Materials and methods

This multisite study was approved by the institutional review board (IRB) at the University of California, Davis as the lead site, and the IRBs at the University of California Irvine, Los Angeles, San Diego, and San Francisco as collaborating sites. The IRBs waived the requirement for informed consent for participation in the study.

### *Study design and setting*

This was a matched case-control study of all eligible discharges from October 1, 2012 through September 30, 2015 at the five University of California academic medical centers. We chose the start date based on the availability of data from all sites and the end date based on the retirement of the International Classification of Diseases, ninth Revision, Clinical Modification (ICD-9-CM) in the United States. Each center participated voluntarily. We defined cases as hospitalizations during which PRF was diagnosed within the first 5 d following the index operation ("early PRF"). We focused on early PRF because this time period is consistent with that of prior studies[4,10,18-21] and because PRF that occurs later plausibly involves different, less easily modifiable risk factors. We selected all hypothesized exposures (predictor variables) based on literature review.

### *Study population*

For efficiency, we used hospital administrative data to identify potential cases and controls. We evaluated hospitalization records from all five sites during the study period that met the denominator criteria of the Agency for Healthcare Research and Quality's Patient Safety Indicator 11 (PSI 11, "Postoperative Respiratory Failure"),[22] namely adults age 18 y or older who were admitted for an elective surgical procedure, excluding patients with respiratory failure present on admission; tracheostomy as the index operation; neuromuscular disorders or degenerative neurological disorders (e.g., Guillain-Barre syndrome); an index operation involving the larynx, pharynx, or craniofacial region; an operation involving esophageal resection, lung cancer resection, or lung transplant; admission diagnoses or procedures involving the respiratory or circulatory system; or an obstetrical condition (eTable 1 in the Online Supplement).[22]

#### *Ascertainment of Cases*

Among eligible records, we first selected those that met PSI 11 numerator criteria[22] for verification as possible cases of PRF. A total of 437 possible cases of PRF were identified.[23] Each of these flagged cases was then reviewed by the primary research team (P.R., G.U., J.S.) to confirm objective evidence of PRF. Twenty-three cases were excluded because none of the

following criteria indicating true clinical PRF was present upon review of the health record:

1) arterial oxygen partial pressure (PaO2) <60 mmHg on room air; a ratio of arterial oxygen partial pressure (PaO2) to the fractional inspired oxygen (FiO2) <300;
2) physician documentation of PRF or acute respiratory distress syndrome (ARDS); or
3) physician documentation of one of the following procedures as a result of respiratory compromise, insufficiency, or failure:
   a. unplanned postoperative endotracheal reintubation;
   b. mechanical ventilation for <96 h that began two or more days postoperatively;
   c. continuous mechanical ventilation for >96 h that began any time intraoperatively or postoperatively.[23]

After omitting the 23 false-positive cases, among the remaining 414 flagged cases, PRF occurred within the first five postoperative days (the targeted case definition) in 340 cases (Figure).[23]

### *Matching and verification of controls*

We selected controls from records that met PSI 11 denominator criteria but not the numerator criteria.[22] Because there were far more potential control records than case records available, we matched cases to controls in a 1:1 ratio, randomly selecting the control(s) within strata based on age (by decade) (Supplemental Appendix, Table 2), hospital (Supplemental Appendix, Table 3), and principal ICD-9-CM procedure code (grouped by anatomic region and open *versus* minimally invasive approach using the Healthcare Cost and Utilization Project Clinical Classification Tools and Software[24]; see Supplemental Appendix, Tables 4 and 5). Once matched, each of the flagged controls was reviewed by the primary research team (P.R., G.U., J.S.) to confirm the absence of true clinical PRF as defined previously.

### *Sample size and power analysis*

We assumed that incomplete matching might reduce the number of evaluable cases from 340 to 300. A priori, using methods described by Dupont and Plummer,[25-27] we determined the odds ratio we would be able to detect for a sample size of 300 cases matched 1:1 to controls. We calculated we would be able to detect true odds ratios more extreme than 0.49 or 1.82 in exposed relative to unexposed subjects with power of 80% at an $\alpha$ level of 0.05, assuming a probability of exposure among controls of 20% and a correlation coefficient for exposure between matched cases and controls of 0.2.

### *Instrument development*

Through iterative review and testing, we modified the abstraction instrument from a prior University Healthsystem Consortium PRF benchmarking project[28] for use in this study via the REDCap electronic platform. The final instrument, which we previously published as an online supplement for a multicenter study of the validity of PSI 11,[23] collected information on demographic characteristics, preexisting comorbid conditions (see eAppendix 1. Definitions of Comorbidities, Predictors, and Primary Outcome Variables), preoperative laboratory and radiographic test results, diagnoses and procedures, length of stay, intra- and perioperative management (including ventilator settings, intravenous fluid

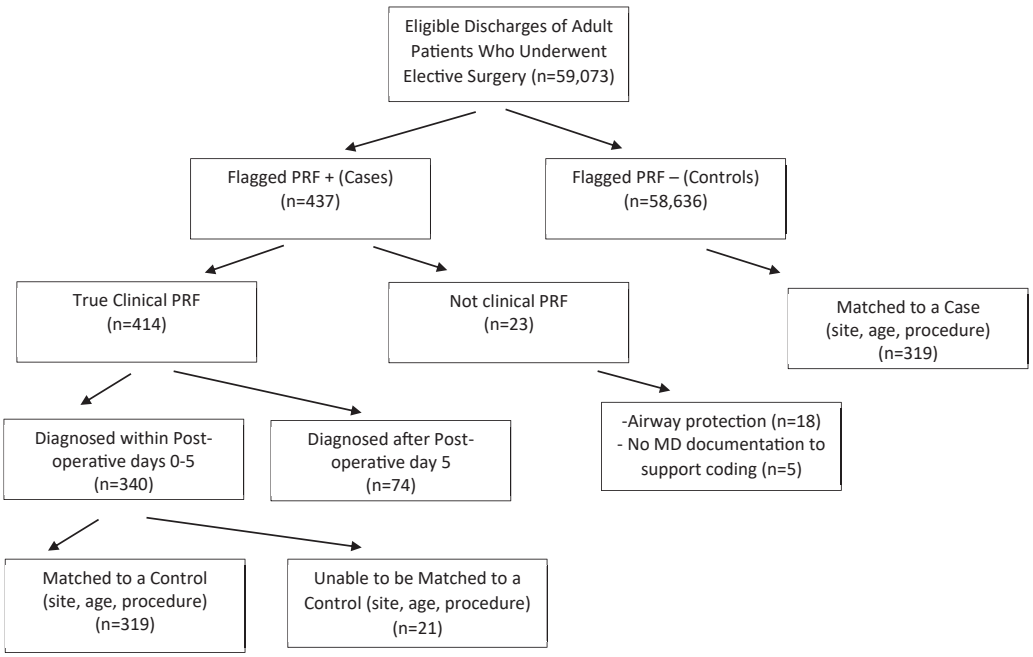


**Fig – Ascertainment of cases and controls. Cases (postoperative respiratory failure confirmed) were matched 1:1 to controls (absence of postoperative respiratory failure confirmed) based on age (by decade), hospital site, and surgical procedure (anatomical location).**

administration, fluid balance, and pain and sedation medication administration), and discharge disposition. We used methodology developed by Vizient, Inc., to determine total costs of care for each encounter, inclusive of direct and indirect costs, from charge data.[29]

### *Data collection*

The data were manually extracted from the health records of each center and entered into a REDCap database. Through a combination of written training materials, teleconferences, and in-person meetings, the principal investigator (J.S.) trained five abstractors in data collection. The principal investigator validated the data abstraction of 100% of the records. Interrater reliability was not explicitly measured, but disagreements after the initial training period were rare.

### *Statistical analysis*

We performed Poisson regression to analyze differences in hospital and intensive care unit length of stay between patients who developed PRF and those who did not, and linear regression to analyze differences in total cost. We performed conditional logistic regression to assess all other variables individually as potential risk factors for PRF. We calculated unadjusted odds ratios and 95% confidence intervals (CIs). We assessed all predictors supported by prior studies and predictors with $P < 0.20$ for collinearity. We excluded all variables with a variance inflation factor $\geq 2.5$ in two-variable regression models from consideration for multivariable analysis.[30] We ranked predictors for inclusion in the multivariable analysis based on odds ratios and analyses of $2 \times 2$ tables (case/control *versus* exposed/nonexposed). In an attempt to mitigate sparse data bias, which produces a bias away from the null and can cause misleading inferences about confounding and effect size, we only advanced variables to multivariable analyses if they had $\geq 20$ observations per cell in the $2 \times 2$ tables.[31]

We developed multivariable conditional logistic regression models using purposeful variable selection[32] and a 10% change-in-estimate procedure[33] to determine if the potential for confounding was present and warranted adjustment. We calculated adjusted odds ratios and 95% confidence intervals, using Stata MP version 15.1 for all analyses.

## Results

With 340 total confirmed cases of early PRF among 59,073 eligible discharges from the five sites, the overall rate of early PRF during the study period was 5.8 cases per 1000 eligible discharges. There were 21 early PRF cases for whom no matching control could be found, leaving a total of 319 early PRF cases matched 1:1 to 319 controls (Figure).

Our total sample ($n = 638$) was 56.4% female, 71.3% white, and had a median age of 62 y (interquartile range [IQR] 51, 70). Most patients had an American Society of Anesthesiologists (ASA) class of III or greater ($n = 468$, 73.4%) with a median of 2 comorbid conditions on admission (IQR 1-3). Operations most often involved open procedures of the abdomen or pelvis ($n = 266$, 41.7%), followed by open procedures of the head and neck region ($n = 110$, 17.2%). Most patients ($n = 617$, 96.7%) had general anesthesia and were induced with administration of a benzodiazepine ($n = 447$, 70.1%) and a neuromuscular blocking agent ($n = 570$, 89.3%). The most common neuromuscular blocking agent used for induction was rocuronium ($n = 377$, 59.1%); the second most common neuromuscular blocking agent used for induction was succinylcholine ($n = 104$, 16.3%).

Among the 319 cases, 186 (58.3%) met PRF criteria based on physician diagnosis of respiratory failure or ARDS (supported by objective findings), 237 (72.3%) met criteria based on prolonged mechanical ventilation, and 180 (56.4%) met criteria based on postoperative reintubation (categories not mutually exclusive). Defining mutually exclusive categories, 82 (25.7%) of the 319 cases met criteria based solely on physician diagnosis of respiratory failure or ARDS, 133 (41.7%) met criteria based solely on prolonged mechanical ventilation or postoperative reintubation, and 104 (32.6%) met criteria based on both physician diagnosis of respiratory failure or ARDS and prolonged mechanical ventilation or postoperative reintubation. Of the 133 patients who met criteria based only on prolonged mechanical ventilation or postoperative reintubation, 104 (78.2%) required postoperative reintubation for respiratory failure and 29 (21.8%) remained intubated postoperatively and required prolonged mechanical ventilation for respiratory failure.

### *Bivariate analysis*

The median day of diagnosis of early PRF was postoperative day 1 (IQR 0, 2). Cases had higher in-hospital mortality than controls (13.8% *versus* 0.3%; OR 48.3 [95% CI 6.6-352.4]). Cases were also more likely to be discharged functionally dependent on others for their activities of daily living (66.5% *versus* 21.3%; OR 7.52 [95% CI 5.13-11.03]). Adjusting for age, hospital, procedure, ASA class, and total number of comorbidities, the average duration of hospitalization for cases was 3.2 (95% CI 2.6-3.9) times as long as the average duration for controls; the average intensive care unit (ICU) length of stay for cases was 9.2 (95% CI 6.2-13.7) times as long as the average ICU length of stay for controls. Adjusting for age, hospital, procedure, ASA class, and total number of comorbidities, the average total cost of cases was $72,000 (95% CI $58,000-$86,000) greater than that of controls.

Among patient-related factors, male gender, body mass index of 35 or greater, and ASA class of III or greater were associated with increased unadjusted odds of early PRF (Table 1). Several comorbidities present on admission were also associated with increased unadjusted odds of early PRF: chronic kidney disease, chronic obstructive pulmonary disease, cardiac disease, dependent functional status, hypertension, neurologic disease, obstructive sleep apnea, smoking (past or current), and the total number of baseline comorbidities. Comorbidities that were not associated with increased unadjusted odds of early PRF included: daily alcohol use (past or current), asthma, diabetes mellitus (type 1 or type 2), dyspnea, gastroesophageal reflux disease, heart failure, and liver disease.

Procedure-related factors associated with increased unadjusted odds of early PRF included: longer duration of anesthesia and operation; higher intra-operative maximum heart

**Table 1 – Association of clinical and demographic characteristics with postoperative respiratory failure (PRF).**

| Exposure | No PRF, $n = 319$ | PRF, $n = 319$ | Unadjusted odds ratio (95% CI) |
|---|---|---|---|
| Male gender, *n* (%) (Referent: Female) | 122 (38.2) | 156 (48.9) | 1.57 (1.14-2.15) |
| Body mass index, *n* (%) | | | |
| Underweight: < 18.5 | 9 (2.8) | 9 (2.8) | 1.19 (0.46-3.13) |
| Normal weight: 18.5-24.9 | 1007 (31.4) | 86 (27.0) | Referent |
| Overweight: 25-29.9 | 118 (37.0) | 106 (33.2) | 1.06 (0.72-1.57) |
| Class 1 obesity: 30-34.9 | 61 (19.1) | 53 (16.1) | 0.99 (0.63-1.56) |
| Class 2 obesity: 35-39.9 | 15 (4.7) | 28 (8.8) | 2.17 (1.09-4.32) |
| Morbidly obese: >40 | 16 (5.0) | 37 (11.6) | 2.67 (1.37-5.21) |
| ASA class III, IV, or V, *n* (%) (referent: ASA I or II) | 199 (62.4) | 269 (84.3) | 3.52 (2.36-5.26) |
| Chronic kidney disease, *n* (%) | 30 (9.4) | 52 (16.3) | 1.99 (1.22-3.26) |
| Chronic obstructive pulmonary disease, *n* (%) | 14 (4.4) | 30 (9.4) | 2.23 (1.17-4.25) |
| Cardiac disease, *n* (%) | 44 (13.8) | 74 (23.2) | 1.88 (1.25-2.84) |
| Functional status (partially or totally dependent), *n* (%) (referent: Independent) | 7 (2.2) | 21 (6.6) | 3.18 (1.32-7.63) |
| Hypertension, *n* (%) | 153 (48.0) | 182 (57.1) | 1.45 (1.05-2.00) |
| Neurologic disease, *n* (%) | 74 (23.2) | 117 (36.7) | 2.01 (1.42-2.96) |
| Obstructive sleep apnea, *n* (%) | 26 (8.2) | 43 (13.5) | 1.77 (1.06-2.97) |
| Smoker (past or current smoker), *n* (%) (referent: never smoked) | 102 (32.0) | 133 (41.7) | 1.52 (1.10-2.11) |
| Total number of comorbid conditions,* mean (SD) | 2.1 (1.5) | 2.7 (1.7) | 1.26 (1.14-1.40)† |

ASA = American Society of Anesthesiologists.
*Comorbid conditions included in this total: alcohol use, asthma, chronic kidney disease, chronic obstructive pulmonary disease, cardiac disease, dementia, diabetes (treated with oral or injectable antihyperglycemic agents), dysphagia, dyspnea (on admission—at rest or with exertion), functional status (partially or wholly dependent,) gastroesophageal reflux disease, heart failure, home continuous positive airway pressure (CPAP) use, home oxygen use, hypertension, impaired sensorium (acutely confused or delirious), liver disease, neurologic disease, obstructive sleep apnea, respiratory infection (current), sepsis (present on admission), smoking, weight loss (>10% unplanned).
†OR per each additional comorbidity.

rate and end tidal carbon dioxide; higher estimated blood loss; higher intra-operative volume of infused crystalloid, colloid, and blood; higher net positive fluid balance at the end of the operative time and at 24-h after the operation; and higher intra-operative maximum tidal volume, peak inspiratory pressure, and positive end-expiratory pressure (PEEP) (Table 2). The type of anesthesia, use of neuromuscular blockade, type of neuromuscular blockade, lowest mean arterial pressure, and total amount of morphine and/or benzodiazepine equivalent units were not associated with increased unadjusted odds of early PRF.

### *Multivariable analysis*

In the final multivariable conditional logistic regression model (Table 3), factors associated with increased adjusted odds of developing early PRF included: male gender (OR 1.72 [95% CI 1.12-2.63]); ASA class ≥ III (OR 2.85 [95% CI 1.74-4.66]); total number of baseline comorbid conditions, per additional comorbid condition (OR 1.14 [95% CI 1.004-1.30]); longer duration of operation, per additional hour (OR 1.14 [95% CI 1.06-1.22]); higher intraoperative PEEP, per cmH2O increase (OR 1.23 [95% CI 1.13-1.35]); higher intraoperative tidal volume, per mL/kg/ideal body weight increase (OR 1.13 [95% CI 1.004-1.27]); and higher positive net fluid balance at 24-h after the operation, per additional liter (OR 1.17 [95% CI 1.07-1.28]). All two-way interactions between risk factors in the model were tested and found to be statistically nonsignificant.

## Discussion

Clinicians have an intuitive understanding of the causes of PRF, but few studies have addressed which potentially causative factors are empirically observed from PRF cases. Our study identified several preoperative and intraoperative factors associated with increased PRF, suggesting potential interventions. The key findings from our study are that—even after controlling for procedure type and duration, ASA class, and patient comorbidities—intraoperative ventilator settings and 24-h fluid balance were associated with increased likelihood of early PRF. These findings augment a growing body of critical care and surgical literature examining postoperative pulmonary complications. In contrast to prior studies, we focused on the relatively severe complication of respiratory failure (including ARDS) and analyzed risk factors in a heterogeneous adult surgical population.

### *Intraoperative ventilator settings*

The ARDS Network demonstrated improved outcomes in patients with acute lung injury and ARDS treated with protective lung ventilation.[34] The use of protective ventilation of the

**Table 2 – Association of procedure-related characteristics with postoperative respiratory failure (PRF).**

| Exposure | No PRF $n = 319$ | PRF $n = 319$ | Unadjusted Odds ratio (95% CI)* |
|---|---|---|---|
| Duration of anesthesia (h), mean (SD) | 5.24 (2.56) | 7.25 (3.73) | 1.24 (1.17-1.32) |
| Duration of operation (h), mean (SD) | 3.70 (2.23) | 5.28 (3.30) | 1.24 (1.16-1.33) |
| Maximum heart rate (beats/min), mean (SD) | 93 (17) | 96 (19) | 1.01 (1.00-1.02) |
| Maximum end tidal $CO_2$ (mmHg), mean (SD) | 41 (7) | 43 (8) | 1.04 (1.02-1.07) |
| Estimated blood loss (mL) | | | 1.13 (1.06-1.21)† |
| Median (IQR) | 100 (25, 250) | 200 (50, 500) | |
| Mean (SD) | 272 (634) | 1011 (3046) | |
| Weight-normalized estimated blood loss (mL/kg), mean (SD) | 3.7 (8.6) | 14.1 (52.4) | 1.03 (1.01-1.05) |
| Blood transfused (mL) | | | 1.07 (1.03-1.11)† |
| Median (IQR) | 0 (0, 0) | 0 (0, 500) | |
| Mean (SD) | 233 (1137) | 1309 (5130) | |
| Crystalloid administered (L) | | | 1.40 (1.26-1.56) |
| Median (IQR) | 1.80 (1.10, 2.67) | 2.50 (1.50, 4.00) | |
| Mean (SD) | 2.05 (1.38) | 3.03 (2.35) | |
| Colloid administered (mL) | | | 1.16 (1.10-1.23)† |
| Median (IQR) | 0 (0, 250) | 0 (0, 1000) | |
| Mean (SD) | 288 (639) | 835 (1683) | |
| Net fluid balance in operating room (L) | | | 1.29 (1.17-1.42) |
| Median (IQR) | 1.28 (0.79, 2.22) | 2.03 (0.96, 3.83) | |
| Mean (SD) | 1.70 (1.71) | 3.26 (6.57) | |
| Net fluid balance 24 h after operation (L) | | | 1.24 (1.15-1.34) |
| Median (IQR) | 1.11 (0.39, 2.19) | 2.08 (0.69, 3.86) | |
| Mean (SD) | 1.41 (1.92) | 3.33 (7.45) | |
| Maximum intraoperative PEEP (cm water), mean (SD) | 5 (2) | 6 (3) | 1.28 (1.18-1.39) |
| Maximum intraoperative PIP (cm water), mean (SD) | 22 (6) | 28 (7) | 1.13 (1.10-1.16) |
| Maximum intraoperative tidal volume (mL/kg ideal body weight), mean (SD) | 9.1 (1.7) | 9.6 (2.4) | 1.15 (1.05, 1.26) |

PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; mL = milliliter; L = liter; cm = centimeter.
* OR expressed per unit increase in the characteristic, except where otherwise specified (e.g., for PEEP, the odds of PRF increase 28% with each cm of water increase in PEEP).
† OR expressed per each 250 mL of the characteristic.

noninjured lungs of critically ill medical patients has also shown similar benefit.[35,36] Historically, intraoperative ventilation with higher tidal volumes was thought to prevent atelectasis, shunting, and hypoxia during anesthesia.[37] More recently, lower intraoperative tidal volumes have been found to result in better Clinical Pulmonary Infection Scores, lower rates of postoperative pulmonary complications, and better oxygenation in patients with abdominal surgery lasting more than 2 h [38]; reduce the incidence of acute respiratory failure requiring ventilator support and decrease hospital length of stay in patients at intermediate and high-risk for pulmonary complications undergoing abdominal surgery[39]; and limit pulmonary pro-inflammatory changes in the lungs of patients undergoing elective surgery lasting five or more hours.[40] A meta-analysis of 16 studies found that lower intraoperative tidal volumes were associated with a decreased incidence of postoperative lung infection; a secondary analysis of 3 studies found protective lung ventilation with lower tidal volume, PEEP, and recruitment maneuvers reduced the incidence of lung infection, atelectasis, and acute lung injury and also reduced hospital length of stay in patients who were otherwise healthy and underwent general surgery.[41] The evidence supporting intraoperative protective lung ventilation with lower tidal volumes is rapidly expanding. Our findings, which are specific to PRF (as opposed to less severe postoperative pulmonary complications) in a heterogeneous adult surgical population, add to this body of literature.

While the beneficial effect of lower tidal volumes in preventing postoperative pulmonary complications has gained acceptance, the role of PEEP is less clear.[42] Two large studies found that, at lower tidal volumes, higher intraoperative PEEP did not reduce pulmonary complications in the first five postoperative days for obese patients[20] or for patients undergoing open abdominal procedures.[21] These studies grouped together a variety of postoperative pulmonary complications as a composite outcome, but subanalyses examining the most severe component complications did not yield different results.[21] We found that higher intraoperative

**Table 3 – Patient and procedure-related factors associated with PRF in multivariable analysis.**

| Predictor | Adjusted odds ratio |
|---|---|
| Male gender (ref: female) | 1.72 (1.12-2.63) |
| ASA class ≥ III (ref: < III) | 2.85 (1.74-4.66) |
| Number of comorbid conditions (per condition) | 1.14 (1.004-1.30) |
| Duration of operation (per hour) | 1.14 (1.06-1.22) |
| Maximum PEEP (per cm water) | 1.23 (1.13-1.35) |
| Maximum tidal volume (per mL/kg ideal body weight) | 1.13 (1.004-1.27) |
| Net positive fluid at 24 h (per L) | 1.17 (1.07-1.28) |

ASA = American Society of Anesthesiologists; PEEP = positive end-expiratory pressure; cm = centimeter; L = liter.

PEEP was associated with increased risk of PRF but did not find any interaction between high PEEP and either high tidal volume or positive 24-h fluid balance in our sample (i.e., only the main effects were significant). Peak inspiratory pressure was not associated with PRF, but we were unable to analyze other intraoperative ventilator factors of interest, such as driving pressure or other settings, due to lack of documentation.

### *24-h fluid balance*

The critical care literature on fluid balance in medical and surgical patients not yet diagnosed with acute lung injury or ARDS is growing. Several studies describe positive fluid balance as being associated with increased mortality in medical intensive care unit patients[43-45]; fewer studies report on fluid balance in the immediate postoperative period, with conflicting results.[46] The surgical patient population is challenging to study as it is heterogeneous and involves multiple confounding factors. The complex physiological interactions between general and spinal anesthetic medications, ventilator settings, and end-organ perfusion further compound the issue. In a prospective cohort study of 148 noncardiac surgical ICU patients with relatively high APACHE II scores, positive fluid balance was associated with higher mortality.[47] Another prospective cohort study of 144 acute care surgery patients found that achieving negative fluid balance by postoperative day one provided a protective effect against infectious complications and was associated with a nearly 70% reduction in the risk of mortality.[48] A more recent meta-analysis of 23 studies found that goal-directed fluid therapy, as opposed to conventional fluid therapy, in adult patients undergoing elective major abdominal surgery was associated with a reduction in morbidity, hospital length of stay, and ICU length of stay but not mortality.[49] More recently, multimodal, multidisciplinary "Enhanced Recovery After Surgery" protocols (which, among other interventions, promote negative fluid balance) have resulted in reductions in hospital length of stay, complications, readmissions, and costs.[50] We found that a 24-h net positive fluid balance was associated with increased PRF. This represents a potentially modifiable risk factor, especially in patients at high risk due to advanced age or preexisting comorbidities. However, fluid balance is only partly under the direct control of clinicians through fluid and diuretic administration and thus may reflect characteristics of the patient or procedure that cannot be modified. Additionally, any effort to decrease the risk of PRF by promoting a neutral or negative fluid balance must be balanced against the possibility of increasing the risk of other problems, such as acute kidney injury from hypoperfusion.

### *Other factors*

Our findings aligned with those of prior studies regarding the following risk factors for PRF: male gender,[51,52] ASA class of III or greater,[5,6,51-53] total number of comorbid conditions,[6] and duration of the operation.[4] Although some of these factors may be nonmodifiable,[28] we believe that—given the mortality, morbidity, and costs associated with PRF—more research is needed to determine whether some patients may benefit from better optimization of preexisting comorbidities, including possible delay of elective procedures, to better prepare the patient.

To speed application of research findings into practice, future studies should be sufficiently powered to analyze potentially optimizable risk factors associated with specific procedure types. One such recent study identified risk factors for six common procedures and found the risk factors varied by procedure type.[54] The one risk factor that was consistent across all procedures was prolonged procedure time.[54] A few studies involving colorectal and cardiac surgical patients have analyzed the benefits of multimodal "prehabilitation" to optimize such factors as nutrition, exercise, and smoking cessation, but the findings of these are limited.[55,56]

Our results should be interpreted with some caution. For simplicity, we used AHRQ PSI 11 criteria to initially identify possible cases of early postoperative respiratory failure. These criteria exclude most cardiac and peripheral vascular procedures that may have been of interest but were not able to be captured in our patient population. The retrospective case-control design is limited in its ability to establish that observed associations are causal in nature because any tendency by physicians, nurses, and respiratory therapists to document predictors or outcomes unequally between cases and controls could have biased the comparison.[57] We were unable to analyze some variables of interest, such as operative titration of continuous infusions of analgesic and sedative medications (*versus* push doses) and adherence to nursing care bundles (e.g., ventilator weaning trials and early mobility) due to missing or inconsistent documentation. Optimization of the electronic health record to include discrete data fields may prove beneficial for future studies but must be balanced against the documentation burden for providers. Finally, there is the possibility that unmeasured confounders explained the associations between the predictors and the outcome.[58,59]

## Conclusions

Despite these limitations, our findings suggest that three potentially modifiable risk factors—intraoperative ventilator tidal volume, intraoperative PEEP, and degree of 24-h positive fluid balance—are associated with increased odds of

developing early PRF, even accounting for confounders, in a heterogenous adult elective surgery population. These risk factors warrant consideration in informing candidate interventions in future randomized trials aimed at reducing PRF.

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## Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jss.2020.12.043.

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