Positive end-expiratory pressure and risk of postoperative pulmonary complications in patients living at high altitudes and undergoing surgery at low altitudes: a single-centre, retrospective observational study in China

Kaixi Shang, Zongjing Xia, Xiaoli Ye, Zhuoning Li, Chongcong Gong

ABSTRACT

Objectives To examine whether a high positive end-expiratory pressure (PEEP >5 cmH₂O) has a protective effect on the risk of postoperative pulmonary complications (PPCs) in a cohort of patients living at high altitudes and undergoing general anaesthesia.

Design Retrospective, observational study.

Setting A tertiary hospital in China.

Participants Adult Tibetan patients living at high altitudes (≥3000 m) and who went to the low-altitude plain to undergo non-cardiothoracic surgery under general anaesthesia, from January 2018 to April 2020.

Measurements This study included 1905 patients who were divided according to the application of an intraoperative PEEP: low PEEP (<5 cmH₂O, including 0 cmH₂O) or high PEEP (≥5 cmH₂O). The primary outcome was a composite of PPCs within the first 7 postoperative days. The secondary outcomes included reintubation and unplanned intensive care unit (ICU) admission within the first 7 postoperative days and total hospital stays (day).

Results The study included 1032 patients in the low PEEP group and 873 in the high PEEP group. There were no differences in the incidence of PPCs between the high and low PEEP groups (relative risk (RR) 0.913; 95% CI 0.716 to 1.165; p=0.465). After propensity score matching, 643 patients remained in each group, and the incidence of PPCs in the low PEEP group (18.0%) was higher than in the high PEEP group (13.7%; RR 0.720; 95% CI 0.533 to 0.974; p=0.033). There were no differences in the incidence of reintubation, unplanned ICU admission or hospital stays. The risk factors of PPCs derived from multiple regression showed that the application of >5 cmH₂O PEEP during intraoperative mechanical ventilation was associated with a significantly lower risk of PPCs in patients from a high altitude (OR=0.725, 95% CI 0.533 to 0.974; p=0.033). The application of >5 cmH₂O during intraoperative mechanical ventilation in patients living at high altitudes and undergoing surgery at low altitudes may be associated with a lower risk of PPCs. Prospective longitudinal studies are needed to further investigate perioperative lung protection ventilation strategies for patients from high altitudes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ All patients in this large cohort came from high-altitude areas and both propensity score matching and logistic regression were used to mitigate the confounding factors.

⇒ We classified the altitude where the patients came from as high altitude (<3500 m), very high altitude (3500–4500 m) and extremely high altitude (>4500 m) to determine the possible influence of different altitude levels on postoperative pulmonary complications.

⇒ The number of patients who came from extremely high altitude (>4500 m) was small, which may increase the potential for residual confounding.

⇒ Another limitation of this study was that there was no control group of patients living at lower altitudes, so it cannot address whether differences in postoperative pulmonary complications between different levels of positive end-expiratory pressure apply to lowlanders.

INTRODUCTION

At high altitudes (≥2500 m), the human body needs to cope with the decreased partial pressure of oxygen (PaO₂) along with decreased barometric pressure (altitude of Lhasa: 3000–3500 m; PaO₂: 14.55 kPa). Previous studies reported changes in the respiratory and circulatory systems through genetic, endocrine and neurological regulation in highlanders, known as the high-altitude adaptation (HAA). The classic physiological responses include hyperventilation, polycythemia and hypoxic pulmonary vasoconstriction. Conversely, when high-altitude dwellers return to lower altitudes or sea...
levels, the hypoxic compensation state cannot be immediately reversed but is progressive. This multifaceted process that involves the loss of HAA over time is called high-altitude de-adaptation (HADA) and is considered a type of hypoxia–reoxygenation injury. After returning to sea level or low altitude, the impact of hypoxia–reoxygenation on ventilation can cause a series of symptoms such as cough, chest tightening, shortness of breath and even pulmonary atelectasis when the PaO₂ increases with the lower altitude. This hypoxia–reoxygenation injury is a time-dependent process. A cluster-randomised controlled trial reported that hypoxia recovery processes took a long time after descending to the plain (≥100 days), probably due to reoxygenation after hypoxia.

Following the economic development and the convenience of transportation, more and more Tibetan highlanders have been flying to Chengdu Plain (altitude: 500 m; PaO₂: 21.15 kPa) for treatments or surgeries each year. Consequently, many patients have to endure their perioperative period in the HADA process since most of them are admitted to the hospital within 1 month or even 1 week after descending to the plain. The chronic stress of hypoxia at high altitude combined with the acute surgery stress can affect their respiratory, cardiovascular and autonomic nervous systems during HADA, increasing postoperative complications.

In particular, the unrecovered respiratory function might theoretically increase the postoperative pulmonary complications (PPCs) after general anaesthesia. PPCs are the leading cause of postoperative morbidity, mortality and prolonged hospital stay. The incidence of PPCs following thoracic surgery has been reported to be as high as 30%–50%, while the prevalence of PPCs following non-cardiothoracic surgery ranges between 1% and 23% and varies depending on patient-related and surgical factors. A multicentre study based on a non-thoracic surgery perioperative network survey in the USA showed that the rate of PPCs in patients undergoing abdominal, orthopaedic and neurosurgery operations was as high as 33.4%, highlighting the urgency to reduce PPCs among high-altitude populations.

Lung protective ventilation strategies (PVS) effectively minimise ventilator-induced lung injury in an intensive care unit (ICU) and in surgical settings to reduce PPCs. The key components of intraoperative PVS mainly involve low tidal volume (VT), positive end-expiratory pressure (PEEP) and recruitment manoeuvres (RMs). The protective role of low VT is widely accepted, but the precise setting of PEEP remains unclear. In addition, it remains unclear whether the incidence of PPCs in HADA patients increases due to factors such as atelectasis, closure of small airways, reduced lung volume and increased airway resistance after prolonged general anaesthesia. It has not been reported whether the use of PEEP during mechanical ventilation affects the occurrence of PPCs in HADA patients. Consequently, the setting of PEEP needs to be further investigated.

Therefore, this study aimed to investigate whether the use of PEEP during general anaesthesia was associated with decreased PPCs in HADA patients. The results could help improve the perioperative safety of highlanders and reduce postoperative complications.

**METHODS**

**Study design**

This single-centre retrospective study adhered to the applicable 2007 Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

**Patient inclusion**

Adult Tibetan patients treated in West China Hospital Sichuan University Tibet Chengdu Branch Hospital between January 2018 and April 2020 were included in this study. The inclusion criteria were Tibetan highlanders (1) living at high altitudes for more than three generations (altitude ≥3000 m), (2) who underwent non-cardiothoracic surgery under general anaesthesia with endotracheal intubation, (3) >18 years of age, (4) who had American Society of Anesthesiologists (ASA, I: no organic, physiological, biochemical or psychiatric disturbance; II: a patient with mild systemic disease that results in no functional limitation; III: a patient with severe systemic disease that results in functional impairment; IV: severe systemic disease that is a constant threat to life; V: moribund condition in a patient who is not expected to survive with or without the operation; VI: declared brain dead patient whose organs are being harvested for transplantation) physical status I–III, and (5) who had surgical duration ≥1 hour.

The exclusion criteria were those who had (1) single lung ventilation during surgery, (2) prone position or side-lying position during surgery, (3) received lung surgery at any previous time, (4) underwent general anaesthesia or preoperative ventilation support within 30 days before surgery, (5) thoracic or intrathoracic diseases, including thoracic deformity, mediastinal tumours or thoracic tumours, or (6) missing important data, such as living history information, vital signals and parametric ventilation data (figure 1).

**Anaesthesia and intraoperative care**

In the operating room, all patients were monitored continuously using an ECG, pulse oximetry, non-invasive blood pressure, pulse oxygen saturation (SpO₂), body temperature, bispectral index (BIS) electrode, end-tidal partial pressure of carbon dioxide (PETCO₂) and end-tidal gas concentration of volatile anaesthetics. Invasive arterial pressure or central venous pressure was monitored when clinically needed. Anaesthesia was induced intravenously with midazolam (0.03–0.05 mg/kg), sufentanil (0.3–0.6 μg/kg), propofol (1.3–2.6 mg/kg), muscle relaxants (0.3–0.4 mg/kg cisatracurium or 0.5–1.0 mg/kg rocuronium) by the attending anaesthesiologist. Anaesthesia was maintained by sevoflurane and BIS level...
The primary outcome was the incidence of a composite group (PEEP <5 cmH₂O, including PEEP=0 cmH₂O). The intraoperative analgesia was provided with remifentanil (0.1–0.2 µg/kg/min) until the end of surgery. All patients were subjected to single-lumen endotracheal tubes after anaesthesia induction. The ventilation mode was volume-controlled ventilation, VT at 8 mL/kg of predicted body weight, and the inspiratory–expiratory ratio was 1:2. The choice of fraction of inspired oxygen (FiO₂), respiratory rate and PEEP was left to the discretion of the attending anaesthesiologist. The intraoperative restrictive fluid therapy was standardised using crystalloid fluid throughout the surgery at 4–6 mL/kg/hour, while colloid solution was administrated when regarded as clinically necessary. Patients were extubated soon after surgery as appropriate, and then routine reversal of neuromuscular blockade (neostigmine of 0.02–0.05 µg/kg/min) until clinical recovery. The final statistical analysis plan included propensity score matching (PSM) to adjust for differences in baseline characteristics between high PEEP and low PEEP groups. The PSM was classified as high altitude (<3500 m), very high altitude (3500–4500 m) and extremely high altitude (>4500 m). The intraoperative information was obtained from the electronic surgical anaesthesia system (Suzhou Madstone Medical Technology, Co): types of surgery, duration of anaesthesia, intraoperative ventilation parameters, PEEP values, peak airway pressure (Ppeak), VT, PETCO₂, estimated blood loss, urine output and intravenous fluid balance including transfusion of blood products. The types of surgery included orthopaedics, laparotomy, laparoscopic surgery and others (mainly maxillofacial surgery and urological surgery in the lithotomy position). Postoperative information, including postoperative vital signs, PPCs, hospital stay and unplanned ICU admission, was collected. Moreover, according to the medical record information, the patients were evaluated using the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) to assess the risk of PPCs. The ARISCAT score was evaluated according to age, preoperative SpO₂, respiratory infection in the last month, anaemia, duration of surgery and emergency procedure; a score <26 was regarded as low risk, 26–44 as moderate risk and ≥44 as high risk (online supplemental table S2). All statistical analyses were performed using IBM SPSS Statistics V.22.0. All tests were two-tailed, with significance defined as p≤0.05. Continuous and ordinal variables were expressed as mean±SD or median and IQR (25%–75%), and categorical variables as n (%). The Shapiro-Wilk test was first used to test the normal distribution of data, after which Student’s t-test was used for comparison of normally distributed variables, and the Mann-Whitney U test was used for variables with a non-normal distribution. The comparison of categorical variables was conducted with the χ² test or Fisher’s exact test.

The final statistical analysis plan included propensity score matching (PSM) to adjust for differences between high PEEP and low PEEP groups. The PSM model contained age, BMI, ASA physical status, altitude, ARISCAT score and surgery types. High PEEP group patients were propensity score-matched 1:1 to the low PEEP group using the matching algorithm. Residual covariable imbalance after matching was assessed by the Χ² test or Fisher’s exact test.
computing standardised differences, where variables with an absolute standardised difference <10% were considered a strong match. Patients who had the closest PSM in sum were matched in the two groups. Matching was done without replacement and within a tolerance limit of 0.00075. The $X^2$ method was used to compare the paired groups.

Furthermore, we analysed the association of intraoperative PEEP with the risk of PPCs in the matched cohort. First, the preoperative and intraoperative factors were used as covariables to perform single-factor analysis first. Then, the variables of PEEP, age and single-factor analysis that were meaningful ($p<0.10$) were included in the multivariable logistic regression model analysis, adjusted for age, ASA classification, ARISCAT score for prediction of PPCs, pre-existing pulmonary disease, major preoperative comorbidity and types of surgery.

**Patient and public involvement**

There was no patient or public involvement in the study.

**RESULTS**

**Patient inclusion**

A total of 3708 patients from the Tibetan Plateau who underwent non-cardiothoracic surgery between January 2018 and April 2020 met the inclusion criteria. After excluding cases based on the exclusion criteria, a final set of 1905 patients was included, 1032 of whom were in the high PEEP group and 873 in the low PEEP group (figure 1).

**Unmatched cohort**

The demographic information and preoperative and intraoperative characteristics are shown in tables 1 and 2. There were significant differences in weight, height and living altitude, but no differences in age, sex, ASA class, ARISCAT score, smoking status and major preoperative comorbidity between the two groups. There was a difference in the proportion of laparoscopic surgery between the two groups. In terms of intraoperative parameters, the value of PEEP in the high PEEP group was 5.7±0.8 cmH$_2$O and in the low PEEP group was 2.1±0.7 cmH$_2$O ($p<0.001$) (online supplemental figure S1). The median PIP in the high PEEP group was 5.68±0.9 cmH$_2$O vs 2.47±0.8 cmH$_2$O in the low PEEP group ($p<0.001$) (online supplemental figure S1). The median PIP (peak inspiratory pressure) in the high PEEP group was also higher than in the low PEEP group (17.9±3.0 vs 16.9±3.0; $p<0.001$) (table 2). There were no differences in the other variables between the two groups.

In the matched cohort, the incidence of PPCs within the 7 postoperative days was 18% in the low PEEP group and 13.7% in the high PEEP group (RR 0.720; 95% CI 0.533 to 0.974; $p=0.033$) (table 3). The incidence of pulmonary infection within the first 7 postoperative days was higher in the low PEEP group (11.4%) than in the high PEEP group (7.8%) (RR 0.658; 95% CI 0.451 to 0.961; $p=0.029$). Atelectasis occurred in the low PEEP group and was higher than in the high PEEP group (3.7% vs 1.7%; RR 0.449; 95% CI 0.218 to 0.924; $p=0.026$). There were no significant differences in the individual components of the other PPCs (respiratory failure, pleural effusion, pneumothorax, bronchospasm and aspiration pneumonia). The secondary outcomes, including postoperative reintubation, unplanned ICU admission and hospital stay, were not significantly different between the two groups in the matched cohort.

**Sensitivity analyses**

For the matched cohort of HADA patients, there was a significant protective effect of high PEEP (OR 0.725, 95% CI 0.530 to 0.992; $p=0.044$) in reducing PPCs (figure 2). We evaluated the effect of PEEP on PPCs in patients at different altitudes in the matched cohort. There were no differences in the incidence of PPCs in patients at high altitude (>3500m) (13.9% vs 12.1%, $p=0.525$) nor at extremely high altitude (>4500m) (46.3% vs 44.8%, $p=0.900$) (figure 3). The incidence of PPCs in the low PEEP group was higher than in the high PEEP group (18.2% vs 12.3%, $p=0.033$) in patients at very high altitudes (3500–4500m) (figure 3). The living history at an extremely high altitude (>4500m) was associated with the risk of PPCs for HADA patients (OR 6.204, 95% CI 3.514 to 10.955; $p<0.001$) (figure 2).
In order to verify the sensitivity of the results, we examined a subgroup analysis of the included factors. After PSM, the effect of PEEP in HADA patients undergoing abdominal surgery revealed a significant protective effect of high PEEP (24.7% vs 10.3%, RR 0.351, 95% CI 0.153 to 0.805; p=0.011) compared with low PEEP in reducing PPCs. Furthermore, the effect of high PEEP in HADA patients with a history of living at high altitudes (3500–4500 m) resulted as a significant protective factor (18.2% vs 12.3%, RR 0.631, 95% CI 0.412 to 0.966; p=0.033), so as age >65 years, ASA classification III, moderate to high risk and COPD(chronic obstructive pulmonary disease) history (figure 3).

DISCUSSION
This cohort study investigated the association between PEEP and PPCs after general anaesthesia in patients living at high altitudes. The PSM data showed that the application of high PEEP (≥ 5 cmH2O) during intraoperative mechanical ventilation was associated with a significantly lower risk of PPCs in perioperative period with HADA.
Mechanical ventilation during general anaesthesia can deform the lung parenchyma and cause lung injuries such as volutrauma, barotrauma and biotrauma, which can precipitate the development of PPCs. The common physiological basis of PVS is preventing excessive expansion of the alveoli and reducing the repeated opening and closing of the alveoli, thus minimising lung injuries caused by mechanical ventilation. Although low VT can improve lung compliance and reduce inflammatory mediators, ventilation with only low VT might reduce the end-expiratory lung volume (EELV) after anaesthesia induction and increase the areas of atelectasis. The loss of EELV contributes to preventing part of the collapsed alveoli from opening, further leading to atelectasis. Moreover, some studies showed that individualised PEEP determined by maximal respiratory compliance significantly reduced postoperative atelectasis. Nonetheless, some other studies argued that PEEP did not show benefits for PPCs. For example, a large trial of high versus low PEEP during general anaesthesia for open abdominal surgery showed no differences in the development of PPCs with either high or low levels of PEEP (≥2 vs 12 cmH₂O). Another large trial that included obese patients undergoing surgery under general anaesthesia with a higher level of PEEP (12 cmH₂O) and alveolar RMs revealed no differences in reducing PPCs compared with a lower level of PEEP (4 cmH₂O) either.

Nevertheless, all of the above studies on lung PVS during general anaesthesia have focused on populations in the plains. At present, there are about 83 million people around the world living at altitudes ≥2500 m, and they at some point will need specialised surgical interventions. Faced with such a large population base, it is necessary to investigate enhanced recovery after surgery (ERAS) and perioperative safety of the highlanders in combination with the special physiological changes. To the best of our knowledge, there are no studies on perioperative lung PVS in patients living at high altitudes. The results of our study showed that PEEP was associated with a lower risk of PPCs, and it may reduce the incidence of PPCs in patients from high altitudes. It could be because the occurrence and progression of HADA involve damage from hypoxia and reoxygenation leading to respiratory, haematological and cardiovascular system abnormalities that are observed.

## Table 2

| Types of surgery     | Unmatched patients | Matched patients | P value |
|----------------------|--------------------|------------------|---------|
|                      | Low PEEP (n=1032)  | High PEEP (n=873) |         |
|                      | Low PEEP (n=643)   | High PEEP (n=643) |         |
|                      | P value            |                  |         |
|                      | 0.529              | 0.669            |         |
| Orthopaedic          | 566 (54.8%)        | 444 (50.9%)      | 0.091   |
|                      | 339 (52.7%)        | 324 (50.4%)      | 0.403   |
| Laparotomy           | 144 (14.0%)        | 117 (13.4%)      | 0.727   |
|                      | 97 (15.1%)         | 87 (13.5%)       | 0.426   |
| Laparoscopy          | 128 (12.4%)        | 141 (16.2%)      | 0.019   |
|                      | 83 (12.9%)         | 105 (16.3%)      | 0.082   |
| Others               | 194 (18.8%)        | 171 (19.6%)      | 0.663   |
|                      | 124 (19.3%)        | 127 (19.8%)      | 0.833   |
| Duration of anaesthesia (min) | 165 (130–220)    | 170 (140–225)    | 0.239   |
|                      | 170 (130–225)      | 175 (140–220)    | 0.616   |
| Duration of surgery (min) | 120 (90–170)    | 130 (95–172)     | 0.156   |
|                      | 120 (90–170)       | 120 (100–170)    | 0.441   |
| Intraoperative transfusion | 19 (1.8%)        | 14 (1.6%)       | 0.692   |
|                      | 11 (1.7%)          | 9 (1.4%)         | 0.822   |
| Crystalloids (mL)    | 1000 (700–1200)    | 1000 (700–1200)  | 0.790   |
|                      | 1000 (700–1200)    | 1000 (700–1200)  | 0.687   |
| Colloid solution (mL) | 500 (500–1000)    | 500 (500–1000)  | 0.697   |
|                      | 500 (500–1000)     | 500 (500–1000)   | 0.787   |
| Blood loss (mL)      | 100 (100–200)      | 100 (100–200)    | 0.294   |
|                      | 100 (100–200)      | 100 (100–200)    | 0.306   |
| VCV/PCV              | 747/285            | 610/263          | 0.228   |
|                      | 439/204            | 449/197          | 0.630   |
| Median FiO₂          | 67 (61–73)         | 66 (61–73)       | 0.450   |
|                      | 66 (61–72)         | 65 (60–72)       | 0.214   |
| Median SpO₂          | 100 (100–100)      | 100 (100–100)    | 0.404   |
|                      | 100 (100–100)      | 100 (100–100)    | 0.058   |
| VT (mL)              | 465.8±28.0         | 461.7±30.0       | 0.002   |
|                      | 466.5±28.0         | 465.7±28.0       | 0.563   |
| VT/PBW (mL/kg)       | 8.4±1.0            | 8.5±1.0          | 0.028   |
|                      | 8.4±1.0            | 8.5±1.0          | 0.518   |
| Median PEEP (cmH₂O)  | 2.1±0.7            | 5.7±0.8          | 0.001   |
|                      | 2.5±0.8            | 5.7±0.9          | 0.001   |
| Median PIP (cmH₂O)   | 16.7±2.9           | 18.0±3.0         | 0.001   |
|                      | 16.9±3.0           | 17.9±3.0         | 0.001   |

Data are presented as mean±SD or median and IQR. IQR: M (P25–P75). PBW: predicted body weight; male: kg=50+0.91×(height/cm−152.4); female: kg=45.5+0.91×(height/cm−152.4). FiO₂: fraction of inspired oxygen; PBW, predicted body weight; PCV, pressure-controlled ventilation; PEEP, positive end-expiratory pressure; PIP, Peak Inspiratory Pressure; SpO₂, pulse oxygen saturation; VCV, volume-controlled ventilation; VT, tidal volume.
Table 3  Outcomes within the first 7 days after surgery of unmatched patients and matched patients after propensity scoring

|                      | Unmatched patients | Matched patients |
|----------------------|--------------------|------------------|
|                      | Low PEEP (n=1032)  | High PEEP (n=873) |
|                      | Relative risk (95% CI) | P value  | Low PEEP (n=643) | High PEEP (n=643) | Relative risk (95% CI) | P value |
| Primary outcomes     |                    |                  |                   |                            |                       |        |
| All PPCs             | 176 (17.1%)        | 138 (15.8%)      | 0.913 (0.716 to 1.165) | 0.465                      | 116 (18.0%)          | 88 (13.7%) | 0.720 (0.533 to 0.974) | 0.033 |
| Respiratory failure  | 45 (4.4%)          | 39 (4.5%)        | 1.026 (0.661 to 1.590) | 0.910                      | 23 (3.6%)           | 29 (4.5%) | 1.273 (0.728 to 2.226) | 0.396 |
| Pulmonary infection  | 99 (9.6%)          | 83 (9.5%)        | 0.990 (0.729 to 1.346) | 0.950                      | 73 (11.4%)          | 50 (7.8%) | 0.658 (0.451 to 0.961) | 0.029 |
| Pleural effusion     | 7 (0.7%)           | 5 (0.6%)         | 0.843 (0.267 to 2.667) | 0.711*                     | 3 (0.5%)            | 4 (0.6%) | 1.335 (0.298 to 5.991) | 0.704*|
| Atelectasis          | 37 (3.6%)          | 20 (2.3%)        | 0.631 (0.363 to 1.095) | 0.099                      | 24 (3.7%)           | 11 (1.7%) | 0.449 (0.218 to 0.924) | 0.026 |
| Pneumothorax         | 0                  | 0                |                   |                            | 0                    | 0                |                       |      |
| Bronchospasm         | 4 (0.4%)           | 3 (0.3%)         | 0.886 (0.198 to 3.970) | 1.000*                     | 4 (0.6%)            | 0                | 0.994 (0.988 to 1.000) | 0.124*|
| Aspiration pneumonitis| 0                 | 0                |                   |                            | 0                    | 0                |                       |      |
| Secondary outcomes   |                    |                  |                   |                            |                      |                  |        |
| Reintubation         | 19 (1.8%)          | 11 (1.3%)        | 0.680 (0.322 to 1.438) | 0.310                      | 16 (2.5%)           | 8 (1.2%) | 0.494 (0.210 to 1.162) | 0.099 |
| Unplanned ICU admission | 35 (3.4%)          | 24 (2.7%)        | 0.805 (0.475 to 1.365) | 0.420                      | 24 (3.7%)           | 16 (2.5%) | 0.658 (0.346 to 1.251) | 0.199 |
| Hospital stays (days) | 12 (10–15)         | 12 (10–14)       | 0.180              |                            | 12 (10–15)          | 12 (10–14) | 0.058                  |      |

* Fisher’s exact test.

ICU, intensive care unit; PEEP, positive end-expiratory pressure; PPCs, postoperative pulmonary complications.

In this study, we found that a history of living at extremely high altitudes, there were no special effects on the incidence of PPCs in patients from high altitudes. At present, most scholars take 2500 m as the altitude threshold point for determining whether there are PPCs in patients from high altitudes. However, this study found that even at extremely high altitudes, it is possible to avoid PPCs. The incidence of PPCs in patients from high altitudes who came to our hospital for surgery were from altitudes ≥3000 m, mainly from Lhasa (3650 m) and Nagqu (4500 m). Human adaptation to high altitude leads to HADA, which eventually leads to the damage caused by hypoxia at high altitude. In addition, the incidence of PPCs in patients from high altitudes who returned to lower altitudes is higher than that in patients living at extremely high altitudes. This may be related to the factors related to genetics and physiology of the individual and the PEEP. Although in this study PEEP appeared to have a beneficial effect on the incidence of PPCs, the difference is not significant. Therefore, we assumed that the association between high altitude and PPCs might be related to both genetic and physiological factors. Nevertheless, due to the small number of patients living at extremely high altitudes, there were no significant differences in the secondary outcomes, including the incidence of PPCs in patients from high altitudes who returned to lower altitudes.

In conclusion, although the role of PEEP on postoperative PPCs remains controversial, in this study, the use of PEEP did not change the treatment plan and did not influence the incidence of PPCs in patients from high altitudes. This study was conducted at extremely high altitudes (Lhasa). Therefore, this study may not be applicable to patients living at extremely high altitudes (Lhasa). Future studies are needed to verify this conclusion.
altitude classification, we classified the altitude where the patients came from as high altitude, very high altitude and extremely high altitude to determine the possible influence of different altitudes on PPCs. Although many studies on HADA have been previously reported, almost all of them were related to short-term exposure to high altitude, while there are no studies on perioperative patients with HADA. Improvements in the transportation system and economy in Tibet have resulted in more people coming to the plains for medical treatment, usually lasting for several months. These patients who descend from a high-altitude to a low-altitude region for surgical treatment have received little attention thus far. Our study focused on the most common perioperative and postoperative complications to find effective ways to reduce PPCs and promote perioperative safety and ERAS.

Also, there are some limitations to this study. First, although this may be a geographical limitation, the number of patients who came from extremely high altitude (>4500 m) was small, which may cause the potential for residual confounding. Second, 761 patients were excluded because of missing data, and 619 patients were unmatched by PSM and excluded, which could introduce biases. Third, the incidence of pulmonary hypertension was not examined since it was not systematically screened during the study period. Fourth, our study included patients undergoing non-cardiothoracic surgery and general anaesthesia rather than a fixed type of surgery. The number of patients who came from high altitudes was so few that choosing a single surgical type would further reduce the number of participants. Nonetheless, the bias was minimised by removing cardiothoracic surgery. Finally, there was no control group of patients living at lower altitudes, and the study is only applicable to high-altitude populations in the clinical setting of our centre, which cannot answer the question of whether the difference in PPCs between different PEEP levels applies to lowlanders.

The results suggest that a higher PEEP setting is beneficial to prevent PPC in patients from high altitudes undergoing mechanical ventilation. This finding, of course, needs to be viewed in light of the inherent limitations of the study design, as mentioned above. As there is no control group of patients living at lower altitudes, the study can also not answer whether the difference in PPC between different PEEP levels is a characteristic intrinsic to highlanders or whether it also applies to lowlanders. Therefore, a prospective trial including, for example, four groups of patients from either high or low altitudes and with fixed levels of PEEP would be desirable to
corroborate the hypothesis drawn from the present retrospective study.

CONCLUSION

Our study suggests that the application of PEEP ≥5 cmH₂O during intraoperative mechanical ventilation in patients living at high altitudes and undergoing surgery at low altitudes may be associated with a lower risk of PPCs. In addition, a history of living at an extremely high altitude (>4500 m) might be a possible risk factor for PPCs in patients from high altitudes. However, in the clinical environment of our centre, this difference did not change the treatment and outcome of the patients. Therefore, prospective longitudinal studies are needed to further investigate perioperative lung protection ventilation strategies for patients from high altitudes.

Contributors KS conceptualised and resourced the study and was responsible for acquiring funding, developing the methodology and administering the project. ZX supervised the study and reviewed the manuscript. XY, ZL and CG undertook the investigation and validated the data. KS wrote the original draft of this manuscript. XY is the article guarantor, accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish. All authors read and approved the final version of the manuscript.

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Competing interests None declared.

Figure 3  Subgroup analyses of the primary outcome for the matched group after propensity score matching. ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure; PPCs, postoperative pulmonary complications.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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Data availability statement Data are available upon reasonable request. Most of the data relevant to the study are included in the article or uploaded as supplementary information, or available from the Corresponding author (Email: kathyshang@126.com). Data may be reused for future meta-analysis upon reasonable justification of benefit at regional level after permission. Additional information is also available (protocol inclusive of study tool and statistical analysis plan).

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REFERENCES

1. Luks AM, Auerbach PS, Freer L, et al. Wilderness medical society clinical practice guidelines for the prevention and treatment of acute altitude illness: 2019 update. Wilderness Environ Med 2019;30:53–18.

2. School of Human Kinetics PDD, University of British Columbia. Acclimatisation, de-acclimatisation and re-acclimatisation to hypoxia. Vancouver: MacNutt MJ. 2011: 16–23.

3. Grissom CK, Jones BE. Respiratory health benefits and risks of living at moderate altitude. High Alt Med Biol 2018;19:109–15.

4. He B, Hu M, Liang Z, et al. Efficacy of shenqi pollen capsules for high-altitude de-acclimatization syndrome via suppression of the reoxygenation injury and inflammatory response. J Immunol Res 2019;2019:1–12.

5. He B, Wang J, Qian G, et al. Analysis of high-altitude de-acclimatization syndrome after exposure to high altitudes: a cluster-randomized controlled trial. PLoS One 2013;8:e62072.

6. Shih PC, Acharya YV, et al. Comparative genomics and molecular adaptational analysis of arthrobacter from Sikkim Himalaya provided insights into its survivability under multiple high-altitude stress. Genomics 2021;113:151–8.

7. Majmudar AJ, Wong WJ, Simon MC. Hypoxia-Inducible factors and lung hypoxia in preclinical models. Am J Transplant 2010;10:296–309.

8. Odor PM, Bampoe S, Gilhooly D, et al. Perioperative interventions for prevention of postoperative pulmonary complications: systematic review and meta-analysis. BMJ 2020;42:335.

9. Deng Q-W, Tan W-C, Zhao B-C, et al. Intraoperative ventilation strategies to prevent postoperative pulmonary complications: a network meta-analysis of randomised controlled trials. Br J Anaesth 2020;124:324–35.

10. Ball L, de Abreu MG, Schultz MJ, et al. Neumorosus blocking agents and postoperative pulmonary complications. Lancet Respir Med 2019;7:102–3.

11. Colquhoun DA, Leis AM, Shanks AM, et al. A lower tidal volume regimen during one-lung ventilation for lung resection surgery is not associated with reduced postoperative pulmonary complications. J Anesth 2014;28:103–10.

12. Kaufmann K, Heinrich S. Minimizing postoperative pulmonary complications in thoracic surgery patients. Curr Opin Anaesthesiol 2021;34:13–19.

13. Girrbach F, Petroff D, Schulz S, et al. Individualised positive end-expiratory pressure guided by electrical impedance tomography for robot-assisted laparoscopic radical prostatectomy: a prospective, randomised controlled clinical trial. Br J Anaesth 2020;125:373–82.

14. Fernandez-Bustamante A, Frendi G, Sprung J. Postoperative pulmonary complications, early mortality, and hospital stay following Noncardiothoracic surgery: a multicenter study by the periperaoperative research network investigators. JAMA Surg 2017;152:157–66.

15. Sud S, Friedrich JO, Adhikari NKJ, et al. Comparative effectiveness of protective ventilation strategies for moderate and severe acute respiratory distress syndrome. a network meta-analysis. Am J Respir Crit Care Med 2021;203:1366–77.

16. Costa Leme A, Hajjar LA, Volpe MS, et al. Effect of intensive vs moderate alveolar recruitment strategies added to lung-protective ventilation on postoperative pulmonary complications. JAMA 2017;317:1422–32.

17. Santos A, Gomez-Peñalver E, Monge-Garcia MI, et al. Effects on pulmonary vascular mechanics of two different lung-protective ventilation strategies in an experimental model of acute respiratory distress syndrome. Crit Care Med 2017;45:e1157–64.

18. Zhang C, Xu F, Li W, et al. Driving pressure-guided individualized positive end-expiratory pressure in abdominal surgery: a randomized controlled trial. Anesth Analg 2021;133:1197–205.

19. Young CC, Harris EM, Vacchiano C, et al. Lung-protective ventilation for the surgical patient: international expert panel-based consensus recommendations. Br J Anaesth 2019;123:898–913.

20. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007;4:e296.

21. Boden I, Skinner EH, Browning L, et al. Preoperative physiotherapy for the prevention of respiratory complications after upper abdominal surgery: pragmatic, double blinded, multicentre randomised controlled trial. BMJ 2018;360:j5916.

22. Zhang M-Q, Liao Y-Q, Yu H, et al. Ventilation strategies with different inflated oxygen concentration in 2950 m altitude in cardiac surgery (VONTCPB): study protocol for a randomized controlled trial. Trials 2019;20:254.

23. Pramsohler S, Schitz R, Patzak A, et al. Periodic breathing in healthy young adults in normobaric hypoxia equivalent to 3500 m, 4500 m, and 5500 m altitude. J Clin Endocrinol Metab 2019;104:203–6.

24. Li X-F, Jiang D, Jiang Y-L, et al. Comparison of low and high inspiratory oxygen fraction added to lung-protective ventilation on postoperative pulmonary complications after abdominal surgery: a randomized controlled trial. J Clin Anesth 2020;67:110098.

25. Turbel E, Terzi N, Cour M, et al. Positive end-expiratory pressure-induced recruited lung volume measured by volume-pressure curves in acute respiratory distress syndrome: a physiologic systematic review and meta-analysis. Intensive Care Med 2020;46:2212–25.

26. Karapalilis D, Weinberg JS. Intraoperative ventilation strategies to prevent postoperative pulmonary complications: a network meta-analysis. BMJ 2020;42:2212–25.

27. Yoon H-K, Kim BR, Yoon S, et al. The effect of ventilation with individualized positive end-expiratory pressure on postoperative atelectasis in patients undergoing robot-assisted radical prostatectomy: a randomized controlled trial. J Clin Med 2021;10:850.

28. Fu Y, Zhang YW, Gao J, et al. Effects of lung-protective ventilation strategy on lung aeration loss and postoperative pulmonary complications in moderate-risk patients undergoing abdominal surgery. Minerva Anestesiol 2021;87:655–62.

29. Östberg E, Thorisson A, Enlund M, et al. Positive end-expiratory pressure and postoperative atelectasis: a randomized controlled trial. J Anaesthesiology 2021;2021:1–17.

30. PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology, Hennes SNT, Gama de Abreu M, et al. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet 2014;384:495–503.

31. Bluth T, Serpa Neto A, et al. Effect of intraoperative high positive end-expiratory pressure (PEEP) with recruitment maneuvers vs low PEEP on postoperative pulmonary complications in obese patients: a randomized clinical trial. JAMA Surg 2019;2021:1–8.

32. Zhou Z-feng, Fang J-biao, Wang H-fa, et al. Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery: study protocol for a randomized controlled trial. BMJ Open 2019;9:e028464.

33. Azad P, Stobdan T, Zhou D, et al. High-altitude adaptation in humans: from genomics to integrative physiology. J Mol Med 2017;95:1269–82.

34. He B, Li H, Hu M, et al. Association between serum interleukin-17A level and high-altitude deacclimatization syndrome. Mediators Inflamm 2018;2018:1–8.

35. Nistri S, Boccalini G, Bencini A, et al. A new low molecular weight, Mn ii -containing scavenger of superoxide anion protects cardiac muscle cells from hypoxia/reoxygenation injury. Free Radic Res 2015;49:67–77.

36. Lu L, Bai Y, Cheng J, et al. Intermittent short-duration reoxygenation protects against simulated high altitude-induced pulmonary hypertension in rats. Faseb J 2021;35:e21212.

37. Storz JF. High-Altitude adaptation: mechanistic insights from integrated genomics and physiology. Mol Biol Evol 2021;38:2677–91.

38. Zhou Q, Yang S, Luo Y, et al. A randomly-controlled study on the cardiac function at the early stage of return to the plains after short-term exposure to high altitude. PLoS One 2012;7:e31097.

39. Semenza GL, sensing O. Oxygen sensing, hypoxia-inducible factors, and disease pathophysiology. Annu Rev Pathol 2014;9:47–71.
Supplementary materials

Fig. S1. Subgroup analyses of the primary outcome for Matched Group after Propensity Scoring.

![Box plot showing subgroup analyses of PEEP(H2O) for Matched Group before and after Propensity Scoring.](image)
| Complication     | Definition                                                                                                                                                                                                 |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Respiratory failure | When postoperative PaO$_2$ < 60 mmHg on room air, a ratio of PaO$_2$ to inspired oxygen fraction < 300 or arterial oxyhemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy |
| Pulmonary infection | When a patient received antibiotics for suspected respiratory infection and met at least one of the following criteria: new or changed sputum, new or changed lung opacities, fever, leukocyte count $> 12,000 \times 10^9/L^{-1}$ |
| Pleural effusion | Chest x-ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in an upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows |
| Atelectasis      | Lung opacification with a shift of the mediastinum, hilum, or hemidiaphragm toward the affected area and compensatory overinflation in the adjacent nonatelectatic lung |
| Pneumothorax     | Air in the pleural space with no vascular bed surrounding the visceral pleura |
| Bronchospasm     | Newly detected expiratory wheezing treated with bronchodilators |
| Aspiration       | Acute lung injury after the inhalation of regurgitated gastric contents |
Table S2. ARISCAT risk score and grade

| Risk factor                                      | Score |
|--------------------------------------------------|-------|
| **Age (years)**                                  |       |
| ≤ 50                                             | 0     |
| 51-80                                            | 3     |
| > 80                                             | 16    |
| **Pre-operative SpO₂ (%)**                       |       |
| ≥ 96                                             | 0     |
| 91-95                                            | 8     |
| ≤ 90                                             | 24    |
| **Respiratory infection in the last month**       |       |
| No                                               | 0     |
| Yes                                              | 17    |
| **Pre-operative anemia (Hb ≤ 10 g dl⁻¹)**         |       |
| No                                               | 0     |
| Yes                                              | 11    |
| **Surgical incision**                            |       |
| Peripheral                                       | 0     |
| Upper abdominal                                  | 15    |
| Intrathoracic                                    | 24    |
| **Duration of surgery (hr)**                      |       |
| ≤ 2                                              | 0     |
| 2–3                                              | 16    |
| > 3                                              | 23    |
| **Emergency procedure**                          |       |
No                        0  
Yes                       8  

Three levels of risk were indicated by the following cutoffs: < 26 points, low risk; 26–44 points, moderate risk; and ≥ 45 points, high risk. SpO2, pulse oxygen saturation; Hb, hemoglobin.