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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

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ABSTRACT

Objectives To examine whether a high positive end-expiratory pressure (PEEP ≥5 cmH_2O) 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 cmH_2O, including 0 cmH_2O) or high PEEP (≥5 cmH_2O). 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 cmH_2O 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 0.530 to 0.992; p=0.044).

Conclusions The application of PEEP ≥5 cmH_2O 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 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.

Trial registration number Chinese Clinical Trial Registry (ChiCTR2100044260).

INTRODUCTION

At high altitudes (≥2500 m), the human body needs to cope with the decreased partial pressure of oxygen (PaO_2) along with decreased barometric pressure (altitude of Lhasa: 3000–3500 m; PaO_2: 14.55 kPa).[1] 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).[2] The classic physiological responses include hyperventilation, polycythaemia 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.[3] 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 PaO_2 increases with the lower altitude.[4] 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.[5]

Following the economic development and the convenience of transportation, more and more Tibetan highlanders have been flying to Chengdu Plain (altitude: 500 m; PaO_2: 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,[6 7] 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.[8–10] The incidence of PPCs following thoracic surgery has been reported to be as high as 30%–50%,[11 12] while the prevalence of PPCs following non-cardiothoracic surgery ranges between 1% and 23% and varies depending on patient-related and surgical factors.[8 13] 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.[14]

Lung protective ventilation strategies (PVS) effectively minimise ventilator-induced lung injury in an intensive care unit (ICU) and in surgical settings to reduce PPCs.[15 16] The key components of intraoperative PVS mainly involve low tidal volume (VT), positive end-expiratory pressure (PEEP) and recruitment manoeuvres (RMs).[16 17] The protective role of low VT is widely accepted, but the precise setting of PEEP remains unclear.[18 19] 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.[20]

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 (SpO_2), body temperature, bispectral index (BIS) electrode, end-tidal partial pressure of carbon dioxide ($PETCO_2$) 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

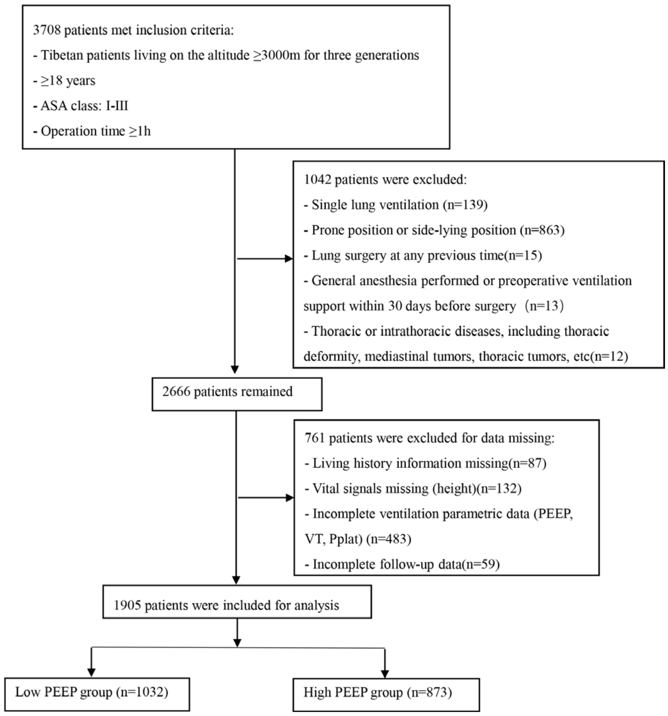

Figure 1 Flow diagram of the study population. ASA, American Society of Anesthesiologists; PEEP, positive end-expiratory pressure; Pplat, plateau pressure; VT, tidal volume.

was maintained at 40–60. 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 (FiO_2), 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 mg/hour) was performed. Patients were observed in the post-anaesthesia care unit (PACU) after extubation. After meeting the PACU standards, patients were transferred to the ward. Patient-controlled intravenous analgesia was administrated for postoperative analgesia. If the numerical rating scale pain score was ≥4 when patients at rest, oral ibuprofen was administered as rescue analgesia.

Exposure and outcomes

According to the application of average intraoperative PEEP values, the included patients were divided into high PEEP group (PEEP ≥5 cmH_2O) and low PEEP group (PEEP <5 cmH_2O, including PEEP=0 cmH_2O). The primary outcome was the incidence of a composite of PPCs (respiratory failure, pulmonary infection, pleural effusion, atelectasis, pneumothorax, bronchospasm and aspiration pneumonitis) (online supplemental table S1) within the first 7 postoperative days.[21 22] The secondary outcomes included the incidence of reintubation and unplanned ICU admission within the first 7 postoperative days, as well as total hospital stay (day).

Data collection

The demographic information was provided by the medical record system (Yonyou Medical Health Information System, Co), including sex, age, living altitude (m), height (cm), weight (kg), body mass index (BMI), ASA physical status, diagnosis, medical history and smoking history. According to the different altitudes, living altitude was classified as high altitude (<3500 m), very high altitude (3500–4500 m) and extremely high altitude (>4500 m).[23] 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 (P_{peak}), VT, $PETCO_2$, 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 SpO_2, 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).[24]

Statistical analysis

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 X^2 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 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_2O and in the low PEEP group was 2.1±0.7 cmH_2O (p<0.001) (online supplemental figure S1). The median P_{peak} in the high PEEP group was higher than in the low PEEP group (18.0±3.0 vs 16.7±2.9; p<0.001). There were no differences in the ventilation mode, FiO_2 and SpO_2. In addition, VT/PBW (predict body weight,male: kg=50+0.91×(height/cm−152.4); female: kg=45.5+0.91×(height/cm−152.4)) was higher in patients from the high PEEP group than in patients from the low PEEP group (p=0.028). There were no differences in terms of surgery, duration of anaesthesia, duration of surgery, intraoperative transfusion, fluid administration and blood loss.

The primary outcome (PPCs) occurred within the first 7 postoperative days in 176 out of 1052 (17.1%) vs 138 out of 873 (15.8%) patients in the low and high PEEP groups, respectively (relative risk (RR) 0.913; 95% CI 0.716 to 1.165; p=0.465) (table 3). There were no significant differences in the individual components of PPCs. Pulmonary infection, which was the most common PPC, occurred in 99 out of 1052 (9.6%) vs 83 out of 873 (9.5%) patients in the low and high PEEP groups, respectively (RR 0.990; 95% CI 0.729 to 1.346; p=0.950). There were no differences in the incidence of postoperative reintubation, unplanned ICU admission and hospital stay between the two groups.

Matched cohort

PSM addressed the differences between the baseline characteristics of the low and high PEEP groups. Of the 873 cases in the high PEEP group, 643 (73.7%) were matched to the low PEEP group, resulting in a matched cohort population of 1286 patients (table 1). In the matched cohort, the average value of PEEP in the high PEEP group was 5.68±0.9 cmH_2O vs 2.47±0.8 cmH_2O 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 matched 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 pneumonitis). 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 (<3500 m) (13.9% vs 12.1%, p=0.525) nor at extremely high altitude (>4500 m) (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 (3500–4500 m) (figure 3). The living history at an extremely high altitude (>4500 m) 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).

Table 1 Demographic information of unmatched patients and matched patients after propensity scoring

	Unmatched patients			Matched patients		
	Low PEEP (n=1032)	High PEEP (n=873)	P value	Low PEEP (n=643)	High PEEP (n=643)	P value
Age (years)	54 (42–64)	52 (39–63)	0.211	52 (39–63)	51 (39–62)	0.399
Male/female	368/664	293/580	0.363	251/392	239/404	0.491
Weight (kg)	69.6±9.3	68.2±9.7	0.002	69.7±9.2	68.9±9.8	0.136
Height (cm)	162 (158–165)	160 (155–165)	0.004	162 (160–165)	162 (160–165)	0.226
BMI (kg/m^2)	26.5 (23.9–28.5)	25.8 (23.8–28.4)	0.054	26.4 (23.8–228.4)	25.8 (23.8–28.4)	0.360
PBW (kg)	55.9±7.1	55.0±7.1	0.008	56.5±6.7	55.8±7.2	0.079
Altitude (m)	3700 (3500–4000)	3800 (3500–4100)	0.001	3800 (3500–4000)	3800 (3500–4000)	0.278
3000–3500	388 (37.6%)	247 (28.3%)	0.001	235 (36.5%)	190 (29.5%)	0.008
3500–4500	590 (66.1%)	577 (66.1%)	<0.001	367 (57.1%)	424 (65.9%)	0.001
>4500	54 (5.2%)	49 (5.6%)	0.715	41 (6.4%)	29 (4.5%)	0.140
ASA class			0.182			0.827
I	87 (8.4%)	60 (6.9%)	0.237	65 (10.1%)	47 (7.3%)	0.075
II	837 (81.1%)	712 (81.6%)	0.846	498 (77.4%)	537 (83.5%)	0.006
III	108 (10.5%)	101 (11.6%)	0.487	80 (12.4%)	59 (9.2%)	0.059
ARISCAT			0.042			0.750
<26	753 (72.9%)	601 (68.8%)	0.054	456 (70.9%)	451 (70.1%)	0.760
26–44	265 (25.7%)	254 (29.1%)	0.106	178 (27.7%)	182 (28.3%)	0.804
>44	14 (1.4%)	18 (2.1%)	0.310	9 (1.4%)	10 (1.6%)	0.501
Preoperative SpO_2	97 (96–98)	97 (96–98)	0.184	97 (96–98)	97 (96–98)	0.701
Smoking			0.992			0.556
Never	733 (71.0%)	618 (70.1%)	0.950	431 (67.0%)	438 (68.1%)	0.677
Current	146 (14.1%)	131 (15.0%)	0.642	102 (15.9%)	108 (16.8%)	0.651
Quit ≥1 month	153 (14.8%)	124 (14.2%)	0.750	110 (17.1%)	97 (15.1%)	0.324
Hypertension			0.861			0.722
No	623 (60.4%)	530 (60.7%)	0.916	410 (63.8%)	411 (63.9%)	0.954
Class I and II	251 (24.3%)	194 (22.2%)	0.305	130 (20.2%)	144 (22.4%)	0.340
Class III	158 (15.3%)	149 (17.1%)	0.329	103 (16.0%)	88 (13.7%)	0.240
COPD	68 (6.6%)	79 (9.0%)	0.055	46 (7.2%)	47 (7.3%)	0.914
Asthma	4 (0.4%)	6 (0.7%)	0.527*	3 (0.5%)	5 (0.8%)	0.726*
Anaemia	29 (2.8%)	27 (3.1%)	0.820	17 (2.6%)	19 (3.0%)	0.735
HAPC	30 (2.9%)	24 (2.7%)	0.946	20 (3.1%)	22 (3.4%)	0.754

Data are presented as mean±SD or median and IQR. IQR: M (P_{25}–P_{75})
Preoperative SpO_2: inhaling air in the operating room.
PBW:predict body weight, male: kg=50+0.91×(height/cm−152.4); female: kg=45.5+0.91×(height/cm−152.4).
*Fisher's exact test.
ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HAPC, high-altitude polycythaemia; PBW, predicted body weight; PEEP, positive end-expiratory pressure; SpO_2, pulse oxygen saturation.

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 cmH_2O) during intraoperative mechanical ventilation was associated with a significantly lower risk of PPCs in perioperative period with HADA.

Table 2 Information on intraoperative characteristics of unmatched patients and matched patients after propensity scoring

	Unmatched patients			Matched patients		
	Low PEEP (n=1032)	High PEEP (n=873)	P value	Low PEEP (n=643)	High PEEP (n=643)	P value
Types of surgery			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	447/196	0.630
Median FiO_2	67 (61–73)	66 (61–73)	0.450	66 (61–72)	65 (60–72)	0.214
Median SpO_2	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±26.0	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 (cmH_2O)	2.1±0.7	5.7±0.8	0.001	2.5±0.8	5.7±0.9	0.001
Median PIP (cmH_2O)	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 (P_{25}– P_{75}).
PBW: predict body weight, male: kg=50+0.91×(height/cm−152.4); female: kg=45.5+0.91×(height/cm−152.4).
FiO_2, fraction of inspired oxygen; PBW, predicted body weight; PCV, pressure-controlled ventilation; PEEP, positive end-expiratory pressure; PIP, Peak Inspiratory Pressure; SpO_2, pulse oxygen saturation; VCV, volume-controlled ventilation; VT, tidal volume.

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 and pulmonary complications.[25] Therefore, in theory, low VT ventilation needs to be combined with PEEP to reduce PPCs. Currently, there are numerous studies on the association between intraoperative ventilator settings during general anaesthesia and the occurrence of PPCs. However, the reported results are still controversial, especially for different groups of patients and different types of surgery.[18 26 27] Several randomised controlled trials showed that intraoperative ventilation with increased levels of PEEP (≥5 cmH_2O) could prevent PPCs.[28 29] Moreover, some studies showed that individualised PEEP determined by maximal respiratory compliance significantly reduced postoperative atelectasis.[13 18 27] 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 cmH_2O).[30] Another large trial that included obese patients undergoing surgery under general anaesthesia with a higher level of PEEP (12 cmH_2O) and alveolar RMs revealed no differences in reducing PPCs compared with a lower level of PEEP (4 cmH_2O) either.[31]

Nevertheless, all of the above studies on lung PVS during general anaesthesia have focused on populations in the plains.[32] 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.[33] 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 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 highlanders when they return to lower altitudes.[34] In addition, with reoxygenation, the PaO_2 increases, and hypoxia and reoxygenation injury can induce oxidative stress-related homeostatic dysregulation, which can activate many signalling pathways in neurons and endothelial cells, thus causing a series of lung injuries, especially atelectasis.[35 36] Therefore, during general anaesthesia, the positive pressure ventilation and the use of muscle relaxants enhance alveolar collapse at the end of expiration, especially during long-time operation, which eventually leads to PPCs. Nevertheless, the application of PEEP can relieve barotrauma caused by alveolar collapse. The main role of the application of PEEP is to avoid alveoli collapse at the end of expiration. In fact, this is the effect of PEEP that protects the lungs during general anaesthesia.

In this study, we found that a history of living at an extremely high altitude (>4500 m) is a possible risk factor for PPCs in patients from high altitudes. At present, most scholars take 2500 m as the altitude threshold point for acute mountain sickness.[1] In our study, patients living at altitude >3000 m were included because all patients who came to our hospital for surgery were from altitudes >3000 m, mainly from Lhasa (3650 m), Qamdo (3200 m) and Nagqu (4500 m). Human adaptation to high altitude is related to genetics and physiology. Still, the higher the altitude, the lower the barometric pressure, where medical problems may occur because of the low inspired PaO_2 caused by the reduced barometric pressure.[37] On the contrary, higher altitude and a longer stay at high altitude lead to HADA when individuals descend to plains. The endothelial cells in the lung tissue are damaged under hypoxia, while the damage to the lung is a continuation of the damage caused by hypoxia at high altitudes that occurs after returning to plains.[38] Therefore, we assumed that the association between the incidence of PPCs and altitude might be related to both damages of continued high-altitude hypoxia, a rather common pathophysiological feature of many human diseases, including cardiovascular, respiratory and neurological diseases.[39] Nevertheless, due to the small number of patients living at extremely high altitudes, future studies are needed to verify this conclusion.

Although in this study PEEP appeared to have a beneficial effect on the incidence of PPCs after general anaesthesia in patients from high altitudes, there were no differences in the secondary outcomes, including the indicators which reflect the severity and outcomes of the disease (postoperative reintubation, unplanned ICU admission and hospital stay). These results indicated that the use of PEEP did not change the treatment plan and development of PPCs in patients from high altitudes.

To our knowledge, this study is the first study to examine the associations between patients from high altitude and PPCs. The strength of this study lies in the fact that all patients came from high-altitude areas, and a relatively large number of cases were included; both propensity score matching and logistic regression were used to mitigate the confounding factors. In addition, according to

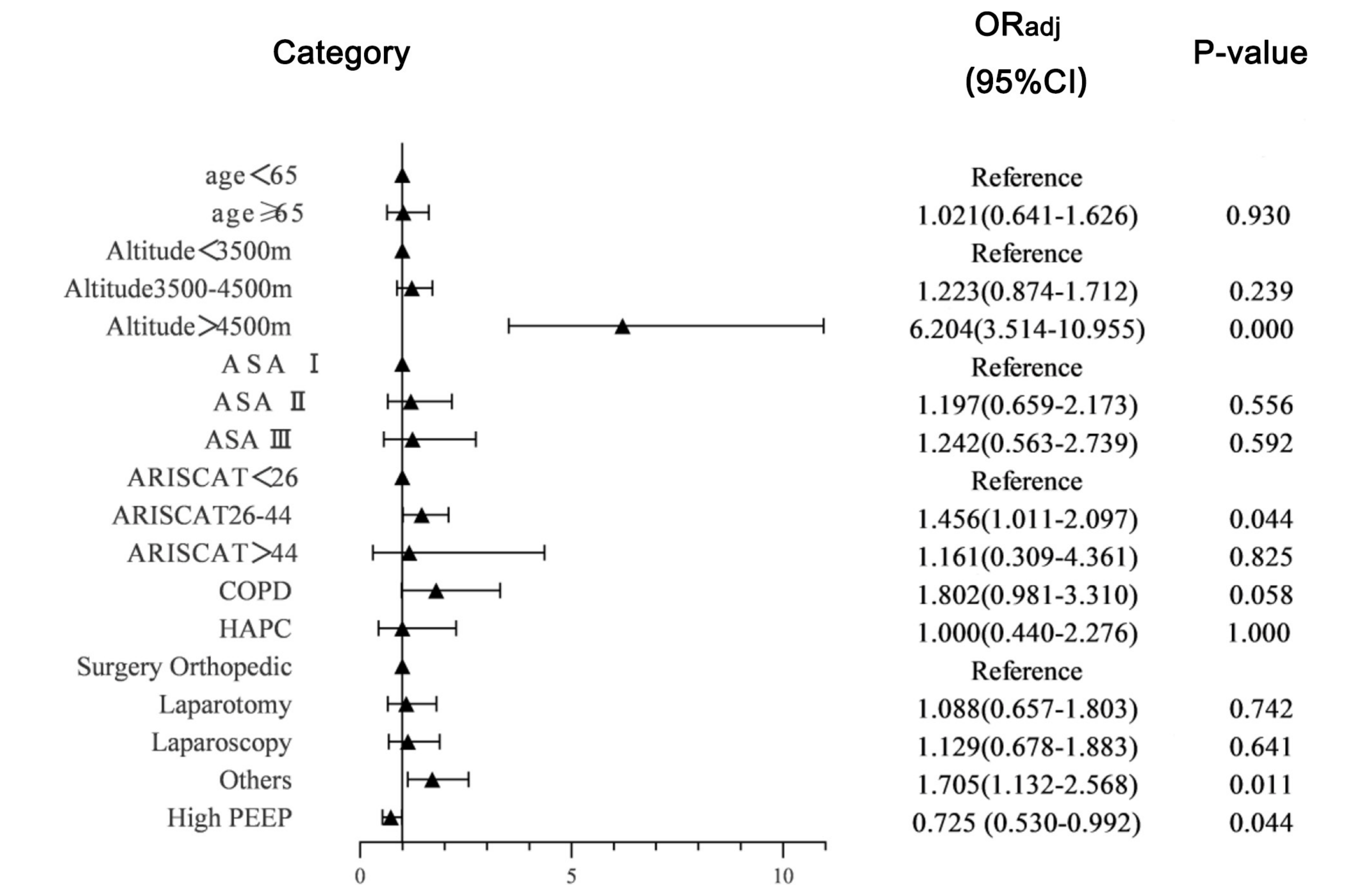

Figure 2 Risk factors for postoperative pulmonary complications derived from multiple regression for the matched group after propensity score matching. ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; HAPC, high-altitude polycythaemia; PEEP, positive end-expiratory pressure.

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

	Low PEEP (NO.PPCs/total)	High PEEP (NO.PPCs/total)	Relative ratio（95%CI）	*P* value
age＜65	82/499(16.4%)	74/525(14.1%)	0.834(0.593-1.174)	0.298
age≥65	34/144(23.6%)	14/118(11.9%)	0.436(0.221-0.858)	0.014
Altitude＜3500m	41/294(13.9%)	30/248(12.1%)	0.849(0.513-1.406)	0.525
Altitude 3500-4500m	56/308(18.2%)	45/366(12.3%)	0.631(0.412-0.966)	0.033
Altitude＞4500m	19/41(46.3%)	13/29(44.8%)	0.941(0.362-2.445)	0.900
ASAI	10/65(15.4%)	5/47(10.6%)	0.655(0.208-2.060)	0.467
ASAII	83/498(16.7%)	76/537(14.2%)	0.824(0.588-1.156)	0.262
ASAIII	23/80(28.7%)	7/59(11.9)	0.334(0.132-0.842)	0.017
ARISCAT＜26	69/456(15.1%)	63/451(14.0%)	0.911(0.629-1.318)	0.620
ARISCAT≥26	47/187(25.1%)	25/192(13.0%)	0.446(0.261-0.761)	0.003
COPD	16/46(34.8%)	7/47(14.9%)	0.328(0.120-0.898)	0.026
Surgery Orthopedic	52/339(15.3%)	44/324(13.6%)	0.867(0.562-1.339)	0.520
Laparotomy	24/97(24.7%)	9/87(10.3%)	0.351(0.153-0.805)	0.011
Laparoscopy	12/83(14.5%)	15/105(14.3%)	0.780(0.218-2.790)	0.752
Others	28/124(22.6%)	20/127(15.7%)	0.641(0.339-1.211)	0.169

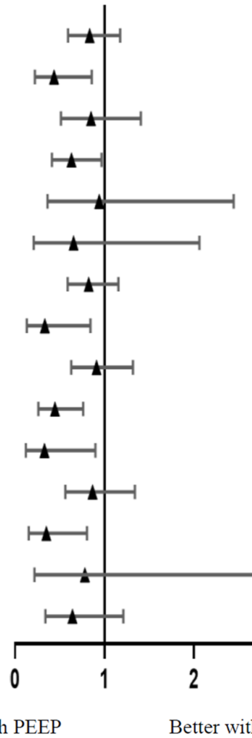

Figure 3 Subgroup analyses of the primary outcome for the matched group after propensity score matching. ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure;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

corroborate the hypothesis drawn from the present retrospective study.

CONCLUSION

Our study suggests that the application of PEEP ≥5 cmH_2O 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 was responsible for data curation and undertook the formal analysis. XY, ZL and CG undertook the investigation and validated the data. KS wrote the original draft of this manuscript. ZX 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.

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.

Ethics approval The study was approved by the Ethics Committee of the West China Hospital Sichuan University Tibet Chengdu Branch Hospital on 23 February 2021 (2021-Research number 11). The requirement for written informed consent was waived by the committee.

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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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