



Correlation of Intraoperative End-Tidal Carbon Dioxide Concentration on Postoperative Hospital Stay in Patients Undergoing Pylorus-Preserving Pancreaticoduodenectomy

Ji-Hoon Park¹ · Hye-Mi Lee^{2,3} · Chang Moo Kang^{4,5} · Kyung Sub Kim⁶ · Chul Ho Jang⁶ · Ho Kyoung Hwang^{4,5} · Jeong-Rim Lee^{2,3}

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Abstract

Background Hypocapnia has been traditionally advocated during general anesthesia, even though it may induce deleterious physiological effects that result in unfavorable outcomes in patients. This study investigated the association between intraoperative end-tidal carbon dioxide (EtCO₂) and length of hospital stay (LOS) in patients who underwent pylorus-preserving pancreaticoduodenectomy (PPPD).

Methods The medical records of 759 patients from 2006 to 2015 were reviewed. The patients were divided into two groups based on the mean EtCO₂ value during general anesthesia: the hypocapnia group (< 35 mmHg) and the normocapnia group (≥ 35 mmHg). The primary outcome was LOS between the groups. Secondary outcomes included the length of intensive care unit (ICU) stay, postoperative 30-day, 1-year, and 2-year mortality, and perioperative factors associated with LOS.

Results A total of 727 patients were finally analyzed. The median LOS of the hypocapnia group was significantly longer than that of the normocapnia group (22 days vs. 18 days, respectively; $p < 0.001$). Postoperative mortality did not differ between the groups. Cox regression analysis revealed that hypocapnia was an independent risk factor for longer LOS (hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.37–1.89; $p < 0.001$). Age and postoperative pancreatic fistula were also risk factors for a longer LOS.

Conclusions It was concluded that low levels of intraoperative EtCO₂ during general anesthesia were associated with an increased LOS for patients undergoing PPPD.

Ji-Hoon Park and Hye-Mi Lee: Co-first author.

✉ Ho Kyoung Hwang
drhkh@yuhs.ac

✉ Jeong-Rim Lee
leejeongrim@gmail.com

¹ Department of Anesthesiology and Pain Medicine, Keimyung University Dongsan Medical Center, 1095 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Korea

² Department of Anaesthesiology and Pain Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea

³ Anesthesia and Pain Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea

⁴ Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea

⁵ Yonsei Cancer Center, Pancreatobiliary Cancer Clinic, Severance Hospital, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea

⁶ Department of Anesthesiology and Pain Medicine, Yonsei University College of Medicine, Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea

Introduction

Pylorus-preserving pancreaticoduodenectomy (PPPD) is one of the most invasive intraabdominal surgeries; it requires a prolonged recovery time after surgery because of its extensive incision, invasiveness, severe postoperative pain, decreased lung function, and postoperative complications [1]. Therefore, it is important to seek out every available opportunity to speed up recovery in order for patients to return to their daily lives as soon as possible after the operation.

Hypocapnia caused by hyperventilation during general anesthesia is a common situation. Traditionally, it has been traditionally advocated, to some extent, because it has been considered to prevent the restoration of spontaneous respiratory efforts and, thus, may reduce the need for muscle relaxants and additional anesthetics [2]. However, hypocapnia has several possible disadvantages in terms of maintaining a normal physiology as it can reduce cerebral blood flow and oxygen delivery [3]. Hypocapnia also causes an increase in the capillary permeability of the lungs, bronchoconstriction, an increase in shunt as a result of decreased lung compliance, and a leftward shift of the hemoglobin dissociative curve [4]. Moreover, it reduces splanchnic blood flow and increases myocardial oxygen demand, hypercoagulability, and the incidence of dysrhythmias [4]. Although the arterial partial pressure of carbon dioxide (PaCO_2) is not monitored continuously, its status is well reflected by end-tidal carbon dioxide (EtCO_2) levels, which are routinely monitored during anesthesia [5]. Despite these shortcomings, EtCO_2 tends to remain as low as ever during surgery [2], and poor clinical outcomes related to hypocapnia have not been sufficiently studied [6, 7].

Prior studies have shown that intraoperative hypocapnia is related to worse outcomes in patients undergoing lower abdominal surgery [6, 7]. However, it is unknown whether deleterious effects from hypocapnia exist in other surgeries, such as PPPD. We hypothesized that hypocapnia in patients undergoing anesthesia for PPPD is associated with worse clinical outcomes compared with patients maintained under normocapnia or hypercapnia.

In this retrospective study, we investigated the effect of intraoperative hypocapnia on hospital stay and mortality in patients undergoing PPPD.

Materials and methods

Ethics

This study was approved by the institutional review board (IRB) of Severance Hospital (no. 4-2019-1164), and the need for informed consent was waived.

Subjects

Data were retrospectively collected from patients who underwent PPPD for a suspicious malignancy at a tertiary university hospital (Severance Hospital) from January 2006 to December 2015. Patients were excluded if they expired during surgery, underwent surgery assisted by laparoscopy or robot, or had undergone cooperation or reoperation.

The patients were divided into two groups based on their mean EtCO_2 values during anesthesia, namely the hypocapnia group (less than 35 mmHg) and the normocapnia group (equal to or greater than 35 mmHg), as proposed by Way and Hill [8].

Perioperative variables

We collected data related to subject age, sex, height, weight, body mass index (BMI), comorbidities, American Society of Anesthesiologists (ASA) classification, tumor location, and malignancy. The collected intraoperative variables were the duration of operation, duration of anesthesia, and peak inspiratory airway pressure (PIP), and EtCO_2 , which was recorded every 15 min in the anesthesia records. Hemodynamic data including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and central venous pressure (CVP) were recorded every 5 min during surgery. Laboratory data, including PaCO_2 from arterial blood gas analysis (ABGA), were also recorded every hour during the operation. The mean values of the variables collected during operation were used for analysis.

Outcomes

The primary outcome was the comparison of postoperative length of hospital stay (LOS) after surgery between the groups. Secondary outcomes included the length of ICU stay; postoperative 30-day, 1-year and 2-year mortality; and incidence of postoperative pancreatic fistula (POPF) as the major postoperative complication [9].

Statistical analysis

Statistical analyses were performed using IBM SPSS[®] Statistics software (ver. 24.0; IBM Corp., Armonk, NY, USA) and SAS (version 9.4, SAS Inc., Cary, NC, USA). For the assumption of a normal distribution, we used the Shapiro–Wilk tests. According to the normality of the data, continuous variables (age, height, weight, body mass index (BMI), duration of operation, duration of anesthesia, intraoperative vital signs, EtCO_2 , and PaCO_2) were

analyzed using Student's *t* test or Mann–Whitney *U* test and were reported as the mean ± standard deviation (SD) or median [interquartile range (IQR)]. All categorical and ranking variables (sex, ASA classification, tumor location, malignancy, mortality, and incidence of POPF) were analyzed using the χ^2 test or Fisher's exact test and were expressed as *n* (%).

Differences in LOS and ICU stay (in days) were calculated using the Kaplan–Meier analysis and log-rank test. Perioperative factors of LOS were analyzed using stepwise Cox regression analysis. Estimates for hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from linear regression models. Independent risk factors for LOS were studied using linear regression analysis. Eighteen variables relating to baseline status were selected for analysis. They included age, sex, operation time, ASA classification, intraoperative vital signs, comorbidities, POPF, and hypocapnia. The variables were tested for selection through stepwise variable selection and were assessed for their impact on LOS. A correlation analysis was conducted to determine the relative influence of EtCO₂ and LOS. A value of *p* < 0.05 was considered to indicate a significant difference for all analyses.

Results

A total of 756 patients were identified, and their medical histories were reviewed. A total of 727 patients were finally included (Fig. 1). Baseline characteristics of the patients are presented in Table 1. The mean EtCO₂ of the hypocapnia group was 33.3 ± 1.9 mmHg versus 36.5 ± 1.2 mmHg in the normocapnia group (*p* < 0.001). The mean PaCO₂ in the hypocapnia group was lower than that in the normocapnia group (32.1 ± 2.6 vs. 33.4 ± 2.4, respectively; *p* < 0.001). Although the body weight in the normocapnia group was greater than that in the hypocapnia group, the BMI was comparable between the groups. The values of SBP, CVP, and PIP were statistically higher in the normocapnia group. There were more patients with ASA classification 3 in the normocapnia group than in the hypocapnia group.

Primary outcome parameters

The patients in the hypocapnia group had a significantly longer hospital stay than those in the normocapnia group (median [IQR], 22 days [16–29] vs. 18 days [13–24];

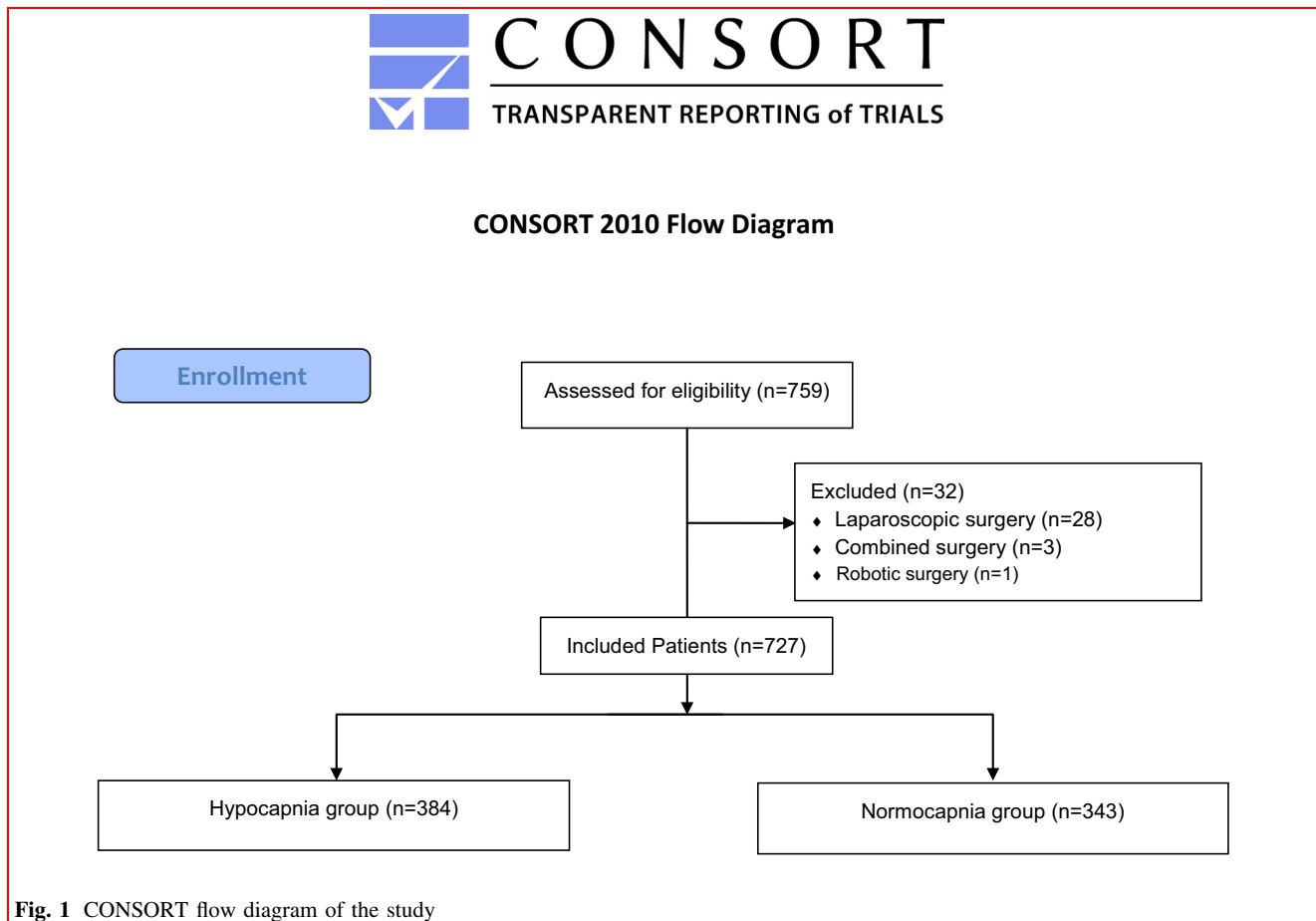


Table 1 Baseline characteristics of the patients included in the two study groups

	Hypocapnia (<i>n</i> = 384)	Normocapnia (<i>n</i> = 343)	<i>p</i> value
<i>Patient enrollment (year)</i>			< 0.001
2006–2007	76 (19.8)	4 (1.2)	
2008–2009	87 (22.7)	25 (7.3)	
2010–2011	93 (24.2)	60 (17.5)	
2012–2013	86 (22.4)	100 (29.1)	
2014–2015	42 (10.9)	154 (44.9)	
Age (years)	64 [55–70]	64 [56–70]	0.838
Height (cm)	162.0 [156.0–168.0]	164.0 [156.9–170.0]	0.115
Weight (kg)	60.0 [53.5–67.9]	63.0 [55.4–68.3]	0.025
Body mass index (kg m ⁻²)	22.9 [21.3–24.8]	23.3 [21.5–25.4]	0.108
<i>Sex</i>			0.072
Male	212 (55)	212 (62)	
Female	172 (45)	131 (38)	
<i>Tumor location</i>			0.796
Pancreas	161 (42)	133 (39)	
Common bile duct	105 (27)	109 (32)	
Ampulla of Vater	88 (23)	83 (24)	
Duodenum	23 (6)	16 (5)	
Gallbladder	7 (2)	2 (1)	
Malignancy	340 (86)	301 (88)	0.462
<i>ASA classification</i>			<0.001
1	38 (10)	23 (7)	
2	297 (77)	225 (66)	
3	47 (12)	92 (27)	
4	2 (1)	3 (1)	
Heart rate (min ⁻¹)	73.7 ± 10.2	74.9 ± 10.2	0.099
Systolic blood pressure (mmHg)	113.4 ± 7.4	115.4 ± 8.2	0.037
Diastolic blood pressure (mmHg)	60.7 ± 5.9	60.7 ± 6.2	0.981
Central venous pressure (mmHg)	6.9 ± 2.3	7.4 ± 2.5	<0.001
Peak airway pressure (cmH ₂ O)	14.3 ± 2.7	16.1 ± 2.9	<0.001
Operation time (min)	419 ± 135	422 ± 104	0.415
EtCO ₂ (mmHg)	33.3 ± 1.9	36.5 ± 1.2	<0.001
PaCO ₂ (mmHg)	32.1 ± 2.6	33.4 ± 2.4	<0.001

Values are presented as the median [IQR] value or the number (%) of patients or mean ± standard deviation. ASA American Society of Anesthesiologists; EtCO₂ end-tidal carbon dioxide; PaCO₂ arterial partial pressure of carbon dioxide

$p < 0.001$; Fig. 2 and Table 2). The correlation between EtCO₂ and LOS showed a negative correlation with $r = -0.249$, $p < 0.001$ (Fig. 3).

Secondary outcome parameters

The length of ICU stay and postoperative 30-day, 1-year, and 2-year mortality did not differ between the groups (Table 2). Cox multivariable analysis revealed that hypocapnia was an independent risk factor for longer LOS (HR, 1.61; 95% CI, 1.37–1.89; $p < 0.001$; Table 3). POPF

was also an independent risk factor for LOS (HR, 1.41; 95% CI, 1.18–1.69; $p < 0.001$), but the incidence of POPF did not differ between the two groups (Tables 2, 3). Age and surgeon's experience were also significantly associated with a longer LOS.

Fig. 2 Kaplan–Meier analysis of the effect of end-tidal carbon dioxide (EtCO₂) on length of hospital stay (LOS)

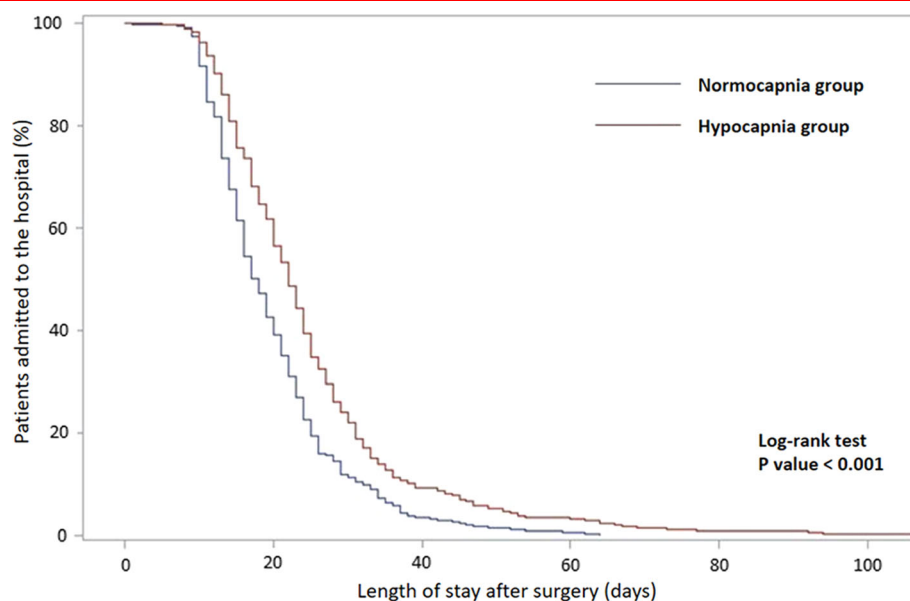


Table 2 Postoperative outcomes after pylorus-preserving pancreatoduodenectomy

	Hypocapnia (<i>n</i> = 384)	Normocapnia (<i>n</i> = 343)	OR (95% CI)	<i>p</i> value
LOS (day)	22 (16–29)	18 (13–24)		<0.001
Length of ICU stays	2 (1–2)	1(1–2)		0.13
30-day mortality	6 (0.8)	2 (0.6)	2.71 (0.54–13.50)	0.225
1-year mortality	47 (12.2)	32 (9.3)	1.36 (0.84–2.18)	0.209
2-year mortality	101 (26.3)	79 (23.0)	1.19 (0.85–1.67)	0.308
POPF	87 (22.7)	92 (26.8)	1.25 (0.89–1.75)	0.193
Vascular resection	5 (1.3)	14 (4.1)	0.31 (0.11–0.87)	0.019

Values are presented as the median [IQR] or the number (%) of patients. *CI* confidence interval; *LOS* length of hospital stay; *ICU* intensive care unit; *POPF* postoperative pancreatic fistula

Discussion

This study shows that patients whose EtCO₂ was less than 35 mmHg during surgery had a longer hospital stay after PPPD, and this mild hypocapnia is an independent risk factor associated with a longer hospital stay (HR 1.61) when compared with patients with EtCO₂ ≥ 35 mmHg.

The length of hospital stay is a valid factor related to quality of care and patients' postoperative functioning [10]. Similar to the results of two other studies [6, 7], our investigation revealed that even mild hypocapnia can result in longer hospital stays and unwanted adverse outcomes. Because all three studies, including ours, were conducted retrospectively, we can surmise that unfavorable physiologic changes due to a low EtCO₂ could result in detrimental outcomes. As mentioned earlier, hypocapnia has

various effects on the whole body, most of which are negative. Hypocapnia, in particular, decreases tissue perfusion, reduces splanchnic blood flow, and affects pulmonary stress, all of which are likely related to the most common complications and factors associated with recovery. A couple of studies investigated the clinically significant effects of EtCO₂ prospectively and demonstrated the harmful effects of hypocapnia in terms of postoperative nausea/vomiting or postoperative delirium [11, 12]. However, it is difficult to prove which aspects of the deteriorating pathophysiology directly affect particular organs or systems.

Meanwhile, mild hypercapnia is considered more beneficial after surgery [6, 13–15], while the mean EtCO₂ in our normocapnic group was just 36.2 mmHg, and no patient was categorized as having hypercapnia. Our results

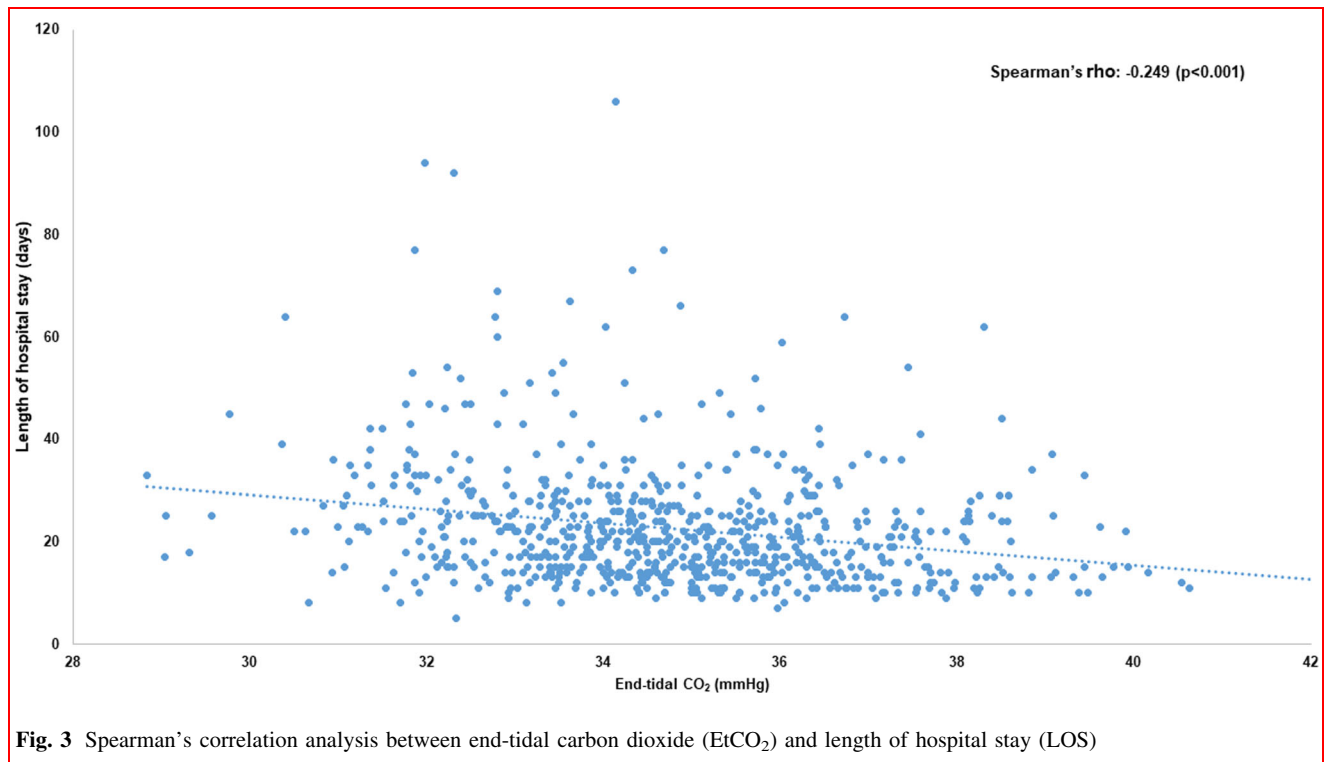


Fig. 3 Spearman's correlation analysis between end-tidal carbon dioxide (EtCO₂) and length of hospital stay (LOS)

show that hypocapnia has a correlation with negative impact on patient outcomes, and whether normocapnia or hypercapnia is more beneficial than normocapnia should be studied further.

In general, EtCO₂ can be monitored simply and noninvasively, and it correlates with the arterial partial pressure of carbon dioxide (PaCO₂); therefore, EtCO₂ is an essential parameter to be monitored during anesthesia. Two previous studies presented and analyzed only EtCO₂ values; the present study added analysis of PaCO₂ values and found that these values were also significantly different between the two groups. However, unlike the gradient between the two variables, which is known to be 2–5 mmHg, it was found that the PaCO₂–EtCO₂ differences were negative and the hypocapnic group was more hypocarbic, while the normocapnic group had less hypocarbia. Reversal of the gradient can be observed normally in pediatric, pregnant, and obese patients, caused by low functional residual capacity (FRC) and decreased total lung compliance, mechanical ventilation with large tidal volumes and low frequency, increased cardiac output and CO₂ production [16–19]. FRC is inevitably reduced in patients undergoing upper abdominal surgery under general anesthesia [20]; therefore, the trend of negative PaCO₂–EtCO₂ in the present study is a probable clinical manifestation. However, EtCO₂ is the average value over the entire operation period, while PaCO₂ is the value obtained a few moments during the operation, particularly at the moment an

anesthesiologist needs to be aware of a patient's blood gas or electrolyte status; therefore, it is not proper to predict that the negative trend of PaCO₂–EtCO₂ differences was maintained during the entire operation and in all patients. In accordance with previous studies, it can be concluded that EtCO₂ value can predict of patients' outcomes, and this result is clinically practical because EtCO₂ is continuously monitored in all anesthetized patients, whereas PaCO₂ requires an invasive technique for determination and is not continuously monitored.

This study was a retrospective study, and it is likely that patient characteristics are not comparable between the two groups. Furthermore, no information was recorded regarding the strategies of the ventilator settings. The concept of lung protective ventilation was not popular about 10–15 years ago; when comparing the annual patient distribution, the number of patients increased from hypocapnia to normocapnia over time. Anesthesiologists might have applied a familiar tidal volume and respiratory rate, rather than a cautious ventilator setting considering both height and weight. As a result, patients who were lightweight may have hyperventilated, resulting in a low EtCO₂ in the hypocapnic group in the present study.

Dony and colleagues studied hospital stay as an indicator of healthcare quality as well as mortality as an indicator of the quality of critical care, and they found an increased 30-day mortality in hypocapnic patients [6]. In our study, mortality was increased for 30-day, 1-year, and

Table 3 Perioperative factors affecting postoperative length of hospital stay

Variables	Univariate			Multiple		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Hypocapnia	1.52	1.32–1.75	<.001	1.61	1.37–1.89	<0.001
Female	0.99	0.85–1.15	0.893			
Age	1.01	1.01–1.02	0.010	1.02	1.01–1.03	< 0.001
Operation time	1.00	1.00–1.01	0.585			
<i>ASA classification</i>						
2	0.84	0.70–1.02	0.067	0.81	0.66–0.98	0.028
3	0.76	0.60–0.96	0.022	0.83	0.63–1.09	0.167
4	0.52	0.21–1.27	0.145	0.66	0.27–1.64	0.367
<i>Surgeon</i>						
1	1.01	0.84–1.23	0.896	0.82	0.67–1.01	0.015
2	2.36	1.90–2.92	<0.001	2.13	1.69–2.67	<0.001
3	1.44	1.13–1.83	0.009	1.21	0.93–1.58	0.831
4	1.31	0.94–1.82	0.145	1.18	0.84–1.66	0.789
Heart rate	1.00	1.00–1.01	0.749			
Systolic blood pressure	1.00	0.99–1.01	0.613			
Diastolic blood pressure	1.00	0.99–1.01	0.875			
Central venous pressure	0.98	0.95–1.01	0.111			
Peak airway pressure	0.97	0.94–1.01	0.060			
Hypertension	0.95	0.83–1.11	0.555			
Diabetes mellitus	0.94	0.81–1.01	0.493			
Pulmonary tuberculosis	0.76	0.57–1.02	0.067			
Hepatitis	0.88	0.57–1.39	0.597			
Asthma	0.43	0.14–1.33	0.141			
Stroke	0.70	0.48–1.01	0.054			
Heart disease	0.78	0.50–1.20	0.249			
POPF	1.33	1.14–1.59	0.001	1.41	1.18–1.69	< .001

Values are presented as odds ratios (95% confidence interval). *HR* hazard ratio; *CI* confidence interval; *ASA* American Society of Anesthesiologists; *POPF* postoperative pancreatic fistula

2-year periods, but there were no statistically significant differences between the normocapnic and hypocapnic groups. First, the 30-day mortality of PPPD was less than 1%, which makes it difficult to demonstrate statistical significance in a few hundred patients. Regarding the 1- and 2-year mortality, they might be affected by disease progression or severity, such as cancer stage and recurrence, rather than by acute postoperative recovery. Alternatively, more patients may be needed to reveal the effect of hypocapnia on this long-term outcome.

POPF remains the main source of major morbidity and mortality after PPPD, which can occur in 13–41% of postoperative patients [21, 22]. Patients who develop POPF are also more likely to develop postoperative complications, including prolonged LOS, wound infection, bile leak, and acute cardiac events [23]. POPF was a significant factor that also led to prolonged LOS in this study

(Table 3); even so, EtCO₂ did not seem to be related to POPF.

This study has several limitations. First, this is a retrospective study that reveals the relationship between phenomena and outcome, and the factors affecting LOS are so complex and diverse that it is difficult to investigate the exact mechanism of EtCO₂ on LOS. Further prospective investigations are warranted to determine if there is a causal relationship. Second, because of the technical limitations of our electronic medical record system, ICU stays were measured on a daily basis rather than on an hourly basis; this may have affected the capacity to discern differences. Third, there was no analysis regarding the influence of other complications on LOS, as the incidence of complications besides POPF was minimal (< 1%) and less than expected. This may be due to insufficient medical records. The development of POPF, the major

complication of PPPD, was well-documented in the medical records and was thus able to be analyzed in this study. Fourth, four surgeons were involved in the study over 10 years. Even though their surgical skills and outcomes were considered comparable and their discharge criteria were standardized, it is difficult to assume that they were perfectly identical. Finally, the LOS of PPPD can differ depending on each country's medical system including insurance, or each institution's policy or the application of the enhanced recovery after surgery (ERAS) protocol. Therefore, there is an issue of external validity. Further studies are needed on the effects of EtCO₂ in institutions with shorter hospital stays.

In summary, intraoperative end-tidal CO₂ status significantly influenced LOS in our cohort of patients undergoing PPPD. This study suggests that preventing hypocapnia during general anesthesia may shorten the length of hospital stay after major abdominal surgery such as PPPD. A prospective study is warranted to demonstrate causality and to determine the best CO₂ management strategy for these and other procedures.

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Compliance with ethical standards

Conflicts of interest All authors declare no conflicts of interest.

Ethical approval This study was approved by the local ethics committee of the hospital, and the need for informed consent was waived.

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