Palliative
Medicine
Reports

Mary Ann Liebert, Inc. publishers

ORIGINAL ARTICLE

Open Access

Predictors of Morphine Efficacy for Dyspnea in Inpatients with Chronic Obstructive Pulmonary Disease: A Secondary Analysis of JORTC-PAL 07

Yoshinobu Matsuda, MD,[1,2,]* Tatsuya Morita, MD,[3] Hirotaka Matsumoto, MD,[4] Keita Hosoi, MD, PhD,[5]
Kayo Kusama, MD,[6] Yasuo Kohashi, MD,[7] Hiroshi Morishita, MD, PhD,[8] Sawako Kaku, MD,[9]
Keisukie Ariyoshi, MMedSc,[10] Shunsuke Oyamada, MMedSc,[11] Yoshikazu Inoue, MD, PhD,[2]
Satoru Iwase, MD, PhD,[12] Takuhiro Yamaguchi, PhD,[13] and Mitsunori Nishikawa, MD[14]

Abstract

Objective: This study aimed to explore the predictors of morphine efficacy in the alleviation of dyspnea in COPD.
Background: Dyspnea is prevalent in patients with chronic obstructive pulmonary disease (COPD) and often persists despite conventional treatment.
Methods: A secondary analysis of a multi-institutional prospective before–after study was conducted focusing on morphine use for alleviating dyspnea in COPD patients. Subjects included COPD patients with dyspnea at seven hospitals in Japan. Patients received 12 mg/day of oral morphine (or 8 mg/day if they had low body weight or renal impairment). Univariate and multivariate logistic regression analyses were performed with numerical rating scale (NRS) score of the current dyspnea intensity in the evening of day 0, Eastern Cooperative Oncology Group Performance Status (ECOG PS; ≤2 or ≥3), age, and partial arterial pressure of carbon dioxide ($PaCO_2$) as independent factors; an improvement of ≥1 in the evening NRS score of dyspnea from day 0 to 2 was the dependent factor.
Results: Thirty-five patients were enrolled in this study between October 2014 and January 2018. Excluding one patient who did not receive the treatment, data from 34 patients were analyzed. In the multivariate analysis, lower $PaCO_2$ was significantly associated with morphine efficacy for alleviating dyspnea (odds ratio [OR] 0.862, 95% confidence interval [CI] 0.747–0.994), whereas the NRS of dyspnea intensity on day 0 (OR 1.426, 95% CI 0.836–2.433), ECOG PS (OR 4.561, 95% CI 0.477–43.565), and patients' age (OR 0.986, 95% CI 0.874–1.114) were not.
Discussion: Morphine can potentially alleviate dyspnea in COPD patients with lower $PaCO_2$. Trial registration: UMIN000015288 (http://www.umin.ac.jp/ctr/index.htm)

Keywords: COPD; dyspnea; morphine; opioid treatment; respiratory illness

[1]Department of Psychosomatic Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan.
[2]Clinical Research Center National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan.
[3]Palliative and Supportive Care Division, Seirei Mikatahara General Hospital, Hamamatsu, Japan.
[4]Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Aamagasaki, Japan.
[5]Department of Respiratory Medicine, Itami City Hospital, Itami, Japan.
[6]Department of Respiratory Medicine, Sakai City Medical Center, Sakai, Japan.
[7]Department of Respiratory Medicine, HARUHI Respiratory Medical Hospital, Kiyosu, Japan.
[8]Department of Respiratory Medicine, Osaka Habikino Medical Center, Habikino, Japan.
[9]Department of Diagnostic Radiology, National Cancer Center Hospital, Tokyo, Japan.
Departments of [10]Data Management and [11]Biostatistics, JORTC Data Center, Tokyo, Japan.
[12]Department of Palliative Medicine, Saitama Medical University, Moroyama, Japan.
[13]Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Japan.
[14]Department of Palliative Care, National Center for Geriatrics and Gerontology, Obu, Japan.

*Address correspondence to: Yoshinobu Matsuda, MD, Department of Psychosomatic Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, 1180 Nagasone-cho, Kita-ku, Sakai, Osaka 591-8555, Japan, E-mail: matsuda.yoshinobu.tx@mail.hosp.go.jp

Introduction

Chronic obstructive pulmonary disease (COPD) is an common lung disease predominantly caused by smoking tobacco.[1] COPD is the fourth cause of death in the world.[2] In Japan, 5.3 million people >40 years and 2.1 million people >70 years have COPD.[3] A majority of COPD patients suffer from dyspnea, which is the most prevalent symptom during the past few months before death.[4,5] In addition to being a distressing symptom for COPD patients,[6] dyspnea is linked to increased anxiety and depression, and has a negative impact on health-related quality of life.[7–10] Despite the availability of treatments such as bronchodilators, inhaled corticosteroids, oxygen therapy, and pulmonary rehabilitation,[11] dyspnea persists in patients with COPD.

Opioids have been reported to be effective to relieve dyspnea in patients with COPD.[12] In fact, COPD guidelines suggest opioids improve dyspnea.[13–16] A multi-institutional prospective before–after original study on the effect of oral morphine on Japanese COPD patients who suffered from dyspnea at rest revealed that morphine had a positive effect on dyspnea. However, some previous studies have reported possible adverse events arising from the use of opioids to treat patients with COPD.[17,18] In addition, a randomized control trial conducted on patients with chronic breathlessness syndrome failed to prove the efficacy of morphine for the treatment of dyspnea.[19] Identifying predictors of the response to morphine can help us personalize symptom management and provide better patient-centered care. In this study, we explored potential factors that could predict the responses to morphine use for alleviating dyspnea in patients with COPD.

Methods

Our protocol was reviewed and approved by the JORTC Protocol Review Committee and the Institutional Review Boards associated with each of the study sites.

Study design and setting

The JORTC-PAL07 study was conducted between October 2014 and February 2018 with 35 COPD patients from seven hospitals in Japan. Eligibility criteria were described in a previously published report.[20] Key inclusion criteria were as follows: inpatients who (1) were diagnosed with COPD using the GOLD 2014 diagnostic criteria; (2) had resting dyspnea despite conventional COPD treatment; (3) were ≥40 years; (4) had a smoking history of 10 pack-years or more; (5) had blood oxygen saturation levels (SpO$_2$) ≥90% with or without oxygen within 14 days before enrollment and partial pressure of carbon dioxide (PaCO$_2$) ≤60 Torr within 28 days before enrollment; and (6) were expected to survive for at least a month. Key exclusion criteria were as follows: patients who (1) had contraindications for morphine; (2) had used any opioid; (3) had pulmonary pathology other than COPD causing dyspnea.

Procedure

The procedure of the original study has been detailed in a previously published report.[20] In brief, a multi-institutional prospective before–after study on oral morphine use in Japanese COPD patients with dyspnea at rest was conducted. A dose of 12 mg of morphine was administered to patients (or a reduced dose of 8 mg if their body weight was <40 kg or their estimated glomerular filtration rate was <60 mL/min).[21] As sustained-release morphine is deemed an off-label drug for noncancer patients in Japan, the patients received 3 mg (or 2 mg) of immediate-release morphine every six hours. Patients' medical records were reviewed to obtain baseline data within two weeks before enrollment.

Current intensity of dyspnea was assessed using an 11-point Likert-type numerical rating scale (NRS) from day 0 to 2 in the mornings (09:00 ± 1 h) and evenings (15:00 ± 1 h).[22,23] Vital signs and opioid-related adverse events were recorded on days 0–2 in the evening. The Richmond Agitation and Sedation Scale was administered on days 0 and 2 in the evening. Adverse events, based on the Common Terminology Criteria for Adverse Events V.4.0, were assessed in the evenings on days 1 and 3. The study was performed in accordance with the Declaration of Helsinki and the Japanese ethical guidelines for clinical research.

Statistical analysis

We analyzed the descriptive statistics for baseline patient characteristics. The primary outcome of the original study was a change in the evening NRS score of dyspnea from day 0 to 2. As a change of 1 on the NRS represents a clinically important difference in chronic breathlessness, it was determined that an improvement of 1 point or more would indicate that morphine is an effective treatment for dyspnea in COPD patients.[24]

Therefore, patients' response to the administration of morphine for dyspnea in this secondary analysis was also defined as showing a reduction of ≥1 in the evening NRS from day 0 to 2. Univariate and multivariate logistic regression analyses were performed using the forced entry methods with the NRS score of dyspnea intensity

on the evening of day 0, the Eastern Cooperative Oncology Group Performance Status (ECOG PS) (≤2 or ≥3), patient age, and $PaCO_2$ as the independent factors, and the response of the patient to the morphine administered for dyspnea as the dependent factor. The four independent factors were selected based on a literature review as follows as well as a discussion among the investigators. The NRS score of dyspnea and patient age were selected based on a previous study.[25] ECOG PS was selected as an independent factor because previous reports had identified a high ECOG PS score as a possible predictor of the efficacy of opioids in the treatment of refractory breathlessness.[26] Finally, we selected $PaCO_2$ as an independent factor because hypercapnia is one of the possible causes of dyspnea and we hypothesized that patients with hypocapnia would respond to morphine to treat dyspnea.[27] We determined $PaCO_2$ as continuous variable because of the exploratory nature of our study. We also conducted a sensitivity analysis using $PaCO_2$ as a binary variable (i.e., ≤45 or >45 Torr). This cutoff point was decided based on a similar cutoff point of $PaCO_2$ used for type 2 chronic respiratory failure in Japan.[28] A two-sided significance level of 0.05 was used for the univariate and multivariate logistic regression analyses. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

The mean age of the patients was 72.9 ± 8.9 years; 94.3% were male; 83% had modified Medical Research Council scale ratings of 3 or 4; and 71.4% received oxygen therapy (Table 1).

Changes NRS score of dyspnea intensity

The NRS score of dyspnea intensity in the evening significantly decreased from 3.0 on day 0 (95% confidence interval [CI] 3.1–4.8) to 2.4 on day 2 (95% CI 1.7–3.1; $p = 0.0002$). Twenty-six patients (76.5%) recorded a decrease of 1 point or more in the NRS score from day 0 to 2, and 8 patients (23.5%) were classified as nonresponders.

Adverse events

There were no apparent changes in the mean scores of opioid-related adverse events and vital signs. One patient experienced grade 3 lung infection not associated with morphine.

Table 1. Baseline Patient Characteristics

	$n = 35$
Age (years), mean (SD)	72.9 (8.9)
Male gender, *n* (%)	33 (94.3)
ECOG performance status, *n* (%)	
0–2	20 (57.1)
3–4	15 (42.9)
History of smoking, *n* (%)	
Former smoker	32 (91.4)
Current smoker	2 (5.7)
Smoking (pack-years), median (IQR)	55.5 (42.0–80.0)
Modified MRC dyspnea scale, *n* (%)	
0–2	6 (17.1)
3–4	29 (82.9)
NRS score of dyspnea intensity in the evening of day 0, *n* (%)	
1–3	18 (51.4)
4–6	10 (28.6)
7–10	7 (20.0)
NRS score of dyspnea intensity in the evening of day 0, median (IQR)	3.0 (2.0–6.0)
GOLD stage, *n* = 29	
I	2 (6.9)
II	3 (10.3)
III	12 (41.4)
IV	12 (41.4)
Total CAT score, mean (SD)	23.1 (6.1)
BMI (kg/m²), mean (SD)	20.4 (3.8)
Postbronchodilator pulmonary function[a]	
FEV_1 (L), mean (SD), *n* = 31	0.87 (0.52)
% FEV_1 (%), mean (SD), *n* = 29	37.3 (20.4)
FEV_1/FVC (%), mean (SD), *n* = 31	38.9 (13.1)
$PaCO_2$ (Torr), mean (SD)	44.0 (8.1)
≥45	14 (40.0)
<45	21 (60.0)
eGFR (mL/min), mean (SD)	77.7 (21.5)
Oxygen delivery device, *n* (%)	
Nasal cannula	23 (65.7)
Oxymizer®	2 (5.7)
Mask	0 (0)
Medication for COPD, *n* (%)	
Long-acting muscarinic antagonist	27 (77.1)
Long-acting β_2-agonist	28 (80.0)
Inhaled corticosteroid	21 (60.0)

[a]Data within one year before enrollment.

BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; MRC, medical research council; NRS, numerical rating scale; $PaCO_2$, arterial partial pressure of carbon dioxide.

Factors predicting the response to morphine for dyspnea

In the univariate logistic regression analysis, lower $PaCO_2$ was significantly associated with response to morphine (odds ratio [OR] 0.889, 95% CI 0.792–0.997), whereas the NRS score of dyspnea intensity on day 0 (OR 1.446, 95% CI 0.908–2.301), ECOG PS (OR 2.571, 95% CI 0.435–15.193), and patient age (OR 0.983, 95% CI 0.897–1.077) were not significantly associated with a response to morphine (Table 2).

Table 2. Univariate Logistic Regression Analysis

Predictors	OR	95% CI	p
NRS of dyspnea intensity on day 0	1.446	0.908–2.301	0.120
ECOG PS (≤2 or ≥3)	2.571	0.435–15.193	0.297
Age	0.983	0.897–1.077	0.711
$PaCO_2$	0.889	0.792–0.997	0.045

ECOG PS, Eastern Cooperative Oncology Group Performance Status; NRS, numerical rating scale; OR, odds ratio.

A sensitivity analysis using $PaCO_2$ as a binary variable revealed that $PaCO_2$ ≤45 was significantly associated with patients' responses to morphine administered to alleviate dyspnea (OR 0.123, 95% CI 0.020–0.758).

In the multivariate logistic regression analysis, lower $PaCO_2$ was significantly associated with the efficacy of morphine use for alleviating dyspnea (OR 0.862, 95% CI 0.747–0.954), but NRS score of dyspnea intensity on day 0 (OR 1.426, 95% CI 0.836–2.433), ECOG PS (OR 4.561, 95% CI 0.477–43.565), and patient age (OR 0.986, 95% CI 0.874–1.114) did not show this association (Table 3). In the sensitivity analysis using $PaCO_2$ as a binary variable, $PaCO_2$ ≤45 was significantly associated with patients' responses to morphine use for alleviating dyspnea (OR 0.074, 95% CI 0.008–0.705; Supplementary Table S1).

Discussion

In this secondary analysis of data from a multi-institutional prospective before–after study, lower $PaCO_2$ was associated with a response to morphine for the alleviation of dyspnea (OR 0.862, 95% CI 0.747–0.954), based on multivariate logistic regression analysis. A sensitivity analysis using a binary $PaCO_2$ variable yielded the same results.

Lower $PaCO_2$ could reflect a better respiratory function and an earlier phase of the disease trajectory compared with a high $PaCO_2$.[29] Dyspnea in COPD patients generally develops in the terminal stage when morphine is used to alleviate it.[5] However, the results from this study indicate that morphine could also be useful in alleviating dyspnea in the early stages.

Table 3. Multivariate Logistic Regression Analysis

Predictors	OR	95% CI	p
NRS of dyspnea intensity on day 0	1.426	0.836–2.433	0.193
ECOG PS (≤2 or ≥3)	4.561	0.477–43.565	0.188
Age	0.986	0.874–1.114	0.824
$PaCO_2$	0.862	0.747–0.994	0.041

Johnson et al. conducted a multicenter retrospective analysis of 213 individual pooled datasets from four clinical trials on the use of an opioid for chronic refractory breathlessness.[25] They reported that higher breathlessness and younger age predicted the efficacy of the opioid in the treatment of breathlessness. However, they did not assess the impact of $PaCO_2$ in their study. To our knowledge, our study was the first to investigate $PaCO_2$ as a factor predicting the response to morphine used to alleviate dyspnea in patients with COPD. To confirm the association, $PaCO_2$ should be assessed at baseline to confirm the relationship between $PaCO_2$ and the response to morphine for dyspnea in future studies. The NRS score of dyspnea intensity on day 0 and patient age were not associated with the efficacy of morphine as a treatment for dyspnea in our study. A small sample size and a narrow distribution of these variables could be potential explanations for these results.

Based on our findings, conducting arterial blood gas analysis to assess $PaCO_2$ might be appropriate to predict the effectiveness of morphine for dyspnea in patients with COPD. However, arterial puncture may cause some complications, such as pain, bleeding, and neuropathy.[30] Therefore, it is important to consider the balance of risks and benefits for each patients when deciding to conduct arterial puncture before using morphine, especially in palliative care settings. In addition, conducting arterial blood analysis may be limited to inpatient setting. In outpatient setting, just trialing whether morphine is effective may be reasonable. Considering these things, it may be reasonable to check the recent $PaCO_2$ data already measured if available.

This study had some limitations. First, this was a before–after study; therefore, the efficacy of morphine was investigated not in terms of change in the level of dyspnea between the group treated with morphine and a placebo group in a randomized control study, but in terms of a change in the level of dyspnea from the baseline to day 2. In addition, a placebo could have overestimated the efficacy of morphine in the treatment of dyspnea among COPD patients. Second, the small sample size could have caused us to overlook some important morphine efficacy predictors. Third, we conducted this study in an inpatient setting. Thus, we need to investigate the predictors of the response to morphine in outpatients setting in the future, where arterial blood gas analysis is unlikely to be available. Fourth, we excluded patients with $PaCO_2$ >60 Torr; however, these patients have most severe dyspnea

and require the management for it. Fifth, the dose of morphine (12 or 8 mg a day) was lower than in previous studies[19,31] although dyspnea was significantly improved by this dose of morphine in our study. Sixth, we assessed the efficacy of the treatment only 2 days after its initiation. This is because we believed a longer study period would have been less feasible, as COPD patients were vulnerable, and their fragile condition could warrant a change in their treatment, including the use of supplemental oxygen or administration of an inhaled bronchodilator. Factors associated with long-term efficacy of the use of morphine in the treatment of dyspnea should be addressed in future studies. Finally, we did not record comorbid conditions. Although we excluded patients with pulmonary pathology other than COPD causing dyspnea, other conditions that could contribute to dyspnea such as heart failure were not analyzed.

Conclusions

Inpatients with lower $PaCO_2$ may respond particularly well to initiation of morphine use for relief of dyspnea; in contrast, the baseline NRS score of dyspnea intensity, performance status, and patient age were not significantly associated with improvement of dyspnea. A large study is needed in the future to confirm the relationship between response to morphine for dyspnea and low $PaCO_2$ in COPD patients.

Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Table S1

References

1. Rabe KF, Watz H: Chronic obstructive pulmonary disease. Lancet 2017; 389:1931–1940.
2. Lozano R, Naghavi M, Foreman K, et al.: Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095–2128.
3. Fukuchi Y, Nishimura M, Ichinose M, et al.: COPD in Japan: The Nippon COPD Epidemiology study. Respirology 2004;9:458–465.
4. Solano JP, Gomes B, Higginson IJ: A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J Pain Symptom Manage 2006;31:58–69.
5. Lynn J, Ely EW, Zhong Z, et al.: Living and dying with chronic obstructive pulmonary disease. J Am Geriatr Soc 2000;48(5 Suppl):S91–S100.
6. Parshall MB, Schwartzstein RM, Adams L, et al.: An official American Thoracic Society statement: Update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 2012;185:435–452.
7. de Voogd JN, Sanderman R, Postema K, et al.: Relationship between anxiety and dyspnea on exertion in patients with chronic obstructive pulmonary disease. Anxiety Stress Coping 2011;24:439–449.
8. Yohannes AM, Junkes-Cunha M, Smith J, et al.: Management of dyspnea and anxiety in chronic obstructive pulmonary disease: A critical review. J Am Med Dir Assoc 2017;18):1096 e1091–1096 e1017.
9. Borge CR, Wahl AK, Moum T: Association of breathlessness with multiple symptoms in chronic obstructive pulmonary disease. J Adv Nurs 2010;66:2688–2700.
10. Tsiligianni I, Kocks J, Tzanakis N, et al.: Factors that influence disease-specific quality of life or health status in patients with COPD: A review and meta-analysis of Pearson correlations. Prim Care Respir J 2011;20:257–268.
11. Johnson MJ, Yorke J, Hansen-Flaschen J, et al.: Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. Eur Respir J 2017;49:1602277.
12. Ekstrom M, Nilsson F, Abernethy AA, et al.: Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. Ann Am Thorac Soc 2015;12:1079–1092.
13. Marciniuk DD, Goodridge D, Hernandez P, et al.: Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: A Canadian Thoracic Society clinical practice guideline. Can Respir J 2011;18:69–78.
14. The Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 Report. www.goldcopd.org (Last accessed June 26, 2020).
15. Young J, Donahue M, Farquhar M, et al.: Using opioids to treat dyspnea in advanced COPD: Attitudes and experiences of family physicians and respiratory therapists. Can Fam Physician 2012;58:e401–e407.
16. Nishikawa M: *Study to Reveal Hospital Support for Old Patients with Terminally Ill Cancer or Chronic Progressing Diseases*. The Research Funding for Longevity Sciences from National Center for Geriatrics & Gerontology Report, 2011.
17. Vozoris NT, Wang X, Austin PC, et al.: Adverse cardiac events associated with incident opioid drug use among older adults with COPD. Eur J Clin Pharmacol 2017;73:1287–1295.
18. Vozoris NT, Wang X, Fischer HD, et al.: Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. Eur Respir J 2016;48:683–693.
19. Currow D, Louw S, McCloud P, et al.: Regular, sustained-release morphine for chronic breathlessness: A multicentre, double-blind, randomised, placebo-controlled trial. Thorax 2020;75:50–56.
20. Matsuda Y, Morita T, Matsumoto H, et al.: Morphine for dyspnoea in chronic obstructive pulmonary disease: A before-after efficacy study. BMJ Support Palliat Care 2019. [Epub ahead of print; doi: 10.1136/bmjspcare-2019-001929.]
21. Currow DC, McDonald C, Oaten S, et al.: Once-daily opioids for chronic dyspnea: A dose increment and pharmacovigilance study. J Pain Symptom Manage 2011;42:388–399.
22. Sessler CN, Gosnell MS, Grap MJ, et al.: The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338–1344.
23. Inouye SK, van Dyck CH, Alessi CA, et al.: Clarifying confusion: The confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941–948.

24. Johnson MJ, Bland JM, Oxberry SG, et al.: Clinically important differences in the intensity of chronic refractory breathlessness. J Pain Symptom Manage 2013;46:957–963.
25. Johnson MJ, Bland JM, Oxberry SG, et al.: Opioids for chronic refractory breathlessness: Patient predictors of beneficial response. Eur Respir J 2013;42:758–766.
26. Johnson MJ, Abernethy AP, Currow DC: Gaps in the evidence base of opioids for refractory breathlessness. A future work plan? J Pain Symptom Manage 2012;43:614–624.
27. Dennis Jensen KP, Jolley C: Mechanisms of breathlessness. In: Claudia Bausewein DC, Johnson M (ed): *Palliative Care in Respiratory Disease*. ERS Monograph. Sheffield, United Kingdom, European Respiratory Society, 2016, pp. 111–p133.
28. *The Japanese Guidelines for the management of Chronic Obstructive Pulmonary Disease, 5th ed*. Tokyo: Medical Review Co., Ltd., 2018.
29. Ahmadi Z, Bornefalk-Hermansson A, Franklin KA, et al.: Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: A population-based prospective study. Respir Res 2014;15:30.
30. Dar K, Williams T, Aitken R, et al.: Arterial versus capillary sampling for analysing blood gas pressures. BMJ 1995;310:24–25.
31. Abernethy AP, Currow DC, Frith P, et al.: Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. BMJ 2003;327:523–528.

Abbreviations Used

BMI = body mass index
CI = confidence interval
COPD = chronic obstructive pulmonary disease
ECOG PS = Eastern Cooperative Oncology Group Performance Status
eGFR = estimated glomerular filtration rate
NRS = numerical rating scale
OR = odds ratio
$PaCO_2$ = partial arterial pressure of carbon dioxide
SD = standard deviation