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ORIGINAL RESEARCH

Management Reality of Female Patients with COPD: A Multicenter Cross-Sectional CAP Study in Japan

Tasuku Yamamoto[1,2], Keiji Oishi[1], Syuichiro Ohata[1], Yoriyuki Murata[1], Yoshikazu Yamaji[1], Maki Asami-Noyama[1], Nobutaka Edakuni[1], Tomoyuki Kakugawa[3], Tsunahiko Hirano[1], Kazuto Matsunaga[1]

[1]Department of Respiratory Medicine and Infectious Disease, Graduate School of Medicine, Yamaguchi University, Ube, Yamaguchi, Japan; [2]Department of Respiratory Medicine, National Hospital Organization Yamaguchi-Ube Medical Center, Ube, Yamaguchi, Japan; [3]Department of Pulmonology and Gerontology, Graduate School of Medicine, Yamaguchi University, Ube, Yamaguchi, Japan

Correspondence: Keiji Oishi, Department of Respiratory Medicine and Infectious Disease, Graduate School of Medicine, Yamaguchi University, 1-1-1 Minami-kogushi, Ube, Yamaguchi, 755-8505, Japan, Tel +81 836 85 3123, Fax +81 836 85 3124, Email ohishk@yamaguchi-u.ac.jp

Background: Reports from Europe and North America suggest that female chronic obstructive pulmonary disease (COPD) patients have a higher symptom burden and mortality than male patients. However, little is known about the management reality of female patients with COPD in Japan.

Patients and Methods: We compared the clinical characteristics of female COPD patients with those of male using the cohort of the COPD Assessment in Practice study, which is a cross-sectional multicenter observational study.

Results: Of the 1168 patients, 133 (11.4%) were female. A history of never smoking was higher in females than males ($p<0.01$). Although there was no difference in age or forced expiratory volume in one second (FEV_1) % predicted between the groups, modified medical research council dyspnea scale (mMRC) and number of frequent exacerbators were higher in females (mMRC≥2: $p<0.01$; number of exacerbations≥2: $p=0.011$). The mean forced vital capacity and FEV_1 values in females were lower than those in males ($p<0.0001$ and $p<0.0001$, respectively). Females were more likely to use long-term oxygen therapy and inhaled corticosteroids than males ($p=0.016$ and $p<0.01$, respectively). The prevalence of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups B, C, D (ABCD GOLD 2017 classification), and E (ABE GOLD 2023 classification) was higher in females than in males.

Conclusion: The disease burden of female patients with COPD is higher than that of male patients in Japan, suggesting the importance of interventions considering female-dominant features such as lower absolute FVC and FEV_1, respiratory failure, and asthma-like conditions.

Keywords: chronic obstructive pulmonary disease, exacerbation, subjective symptoms, gender difference, observational study

Introduction

Epidemiological studies in Europe and the United States have reported that women with chronic obstructive pulmonary disease (COPD) have an increased mortality rate[1,2] and a higher symptom burden than men.[3,4] Additionally, it has become evident that females possess clinically noteworthy characteristics distinct from males in terms of etiology, exacerbating factors such as exposure to causative agents, anatomical and physiological factors, comorbidities. These characteristics are believed to be associated with the heightened symptom awareness observed in females.

Smoking is a major cause of COPD regardless of gender; however, in females, the smoking rate is relatively low,[1,5–7] while they are significantly influenced by factors such as air pollution, the use of biomass fuels for household chores, and exposure to secondhand smoke.[8,9] According to reports from Spain, occupational exposure is associated with COPD risk,[10] and differences in occupations between males and females may influence variations in the etiology of COPD. Report from Korea indicates that in females, there is a higher prevalence of COPD comorbidity among patients with lower household

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income and education levels, suggesting that the high smoking rates in these demographics, as well as a higher prevalence of smoking from a younger age, may be contributing factors.[7] It may be related to the fact that while the smoking rate is decreasing among men, reflecting factors such as increased female participation in society during the past several decades, the smoking rate among women is not declining, which may be contributing to the lack of decrease in mortality rates. COPD related to biomass combustion is a significant public health issue, particularly in developing countries where women are predominantly responsible for household chores. It has been reported that particular matter 2.5 (PM2.5), a major air pollutant, significantly reduces the transition from alveolar type II cells (AT2) to alveolar type I cells (AT1) and decreases lung compliance, leading to emphysema in female mouse models.[11] In COPD associated with biomass combustion, it has been suggested that defects in airway bacterial load and macrophage bacterial phagocytosis play important roles.[12]

In female patients, abnormalities in immune regulation and relatively elevated levels of inflammatory markers are known.[13] There are reports suggesting that several reproductive factors in women, such as age at menarche, number of children, miscarriages, stillbirths, age at menopause, and reproductive hormones, may be associated with the risk of COPD.[13,14] From an anatomical perspective, women are generally known to have differences in lung and thoracic shape and respiratory muscle usage compared to men. Specifically, the smaller airway area leading to increased respiratory resistance and the smaller lung capacity resulting in decreased ventilation efficiency may require higher respiratory effort during peak exercise compared to men.[15] This could potentially be related to the heightened symptom awareness observed in COPD patients.

Comorbidities also differ between male and female patients, with reports indicating higher incidence rates of asthma-like conditions, arthritis, stroke, as well as psychological symptoms such as nervousness, anxiety, and depression in female patients.[1,2,7,16,17] Psychological symptoms are risk factors for COPD exacerbation[18] and are also suggested to be associated with the severity of symptom awareness.[4] While the incidence of cardiovascular disease and emphysema tends to be lower in women compared to men, the incidence of lung cancer is lower in women, and the mortality rate among exacerbation patients is also lower compared to men.[19,20]

Understanding these differences leads to providing more tailored treatment for women. However, female patients with COPD tend to remain undiagnosed and do not receive appropriate intervention.[5] Within this context, there might exist a preconceived notion that COPD primarily affects men, leading to the development of assessment methods and management discussions from a male-oriented perspective, potentially overlooking certain risk factors and the management reality of female patients.

To facilitate a more suitable management of female patients with COPD, it is crucial to elucidate the factors influencing the initiation and severity of COPD in women. As there is a lack of knowledge regarding Japanese women, this study aimed to clarify the clinical characteristics and management realities of female patients with COPD in Japan using a cohort of patients with COPD collected in the past.

Patients and Methods

Subjects

We used a cohort of the COPD Assessment in Practice (CAP) study to compare the clinical characteristics of female COPD patients with those of male COPD patients.[21] In the CAP study, patients with COPD were enrolled from three primary care facilities and 12 secondary care facilities in Japan from April 2013 to May 2014. The inclusion criteria were a clinical diagnosis of COPD (diagnosed as forced expiratory volume in 1s/forced vital capacity (FEV_1/FVC) of <0.7 on postbronchodilator spirometry) and the requirement that patients were in a stable condition and had not experienced exacerbation for four weeks prior to the survey. Patients with other pulmonary diseases or disorders that prevented them from completing the study were excluded. Medical information and patient characteristics, including age, sex, smoking status, disease severity, and current medication information, were obtained from the patients' medical charts.

Protocol

This multicenter cross-sectional study was registered with the University Hospital Medical Information Network (UMIN #000012592) and approved by the Ethics Committee of Wakayama Medical University (approval date: May 7, 2014;

approval #: 1410). Several authors (Tsunahiko Hirano and Kazuto Matsunaga) were affiliated with Wakayama Medical University before transferring to Yamaguchi University in July 2015 due to academic opportunities. The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent for the use of data was obtained from all study participants.

The pulmonary function test procedures complied with the American Thoracic Society/European Respiratory Society guidelines.[22] The post-bronchodilator FVC and FEV_1 were measured using a dry rolling seal spirometer on the same day. Spirometric reference values were reported by the Japanese Respiratory Society for FEV_1.[23] The severity rankings of COPD, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) I–IV, are based on $\%FEV_1$ according to the GOLD guidelines.[24] Dyspnea was evaluated using the modified Medical Research Council (mMRC) scale, which comprises five statements describing the extent of respiratory disability from no disability (grade 0) to almost complete incapacity (grade 4).[25] The GOLD ABCD classification was determined based on GOLD 2017, and the GOLD ABE classification was determined based on GOLD 2023, according to the mMRC and exacerbation history.[24]

Exacerbation was defined as an acute event characterized by worsening of respiratory symptoms beyond normal day-to-day variations and led to a change in medication.[26] The requirement for systemic corticosteroids or antibiotics and the number of hospitalizations due to COPD during the previous 1 year were determined by reviewing medical records,[27] and these data were confirmed through a patient interview.

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation, and categorical variables are presented as numbers and percentages. We compared the clinical parameters of female COPD patients with those of males. Differences in continuous variables between the two groups were determined using the Student's *t*-test or Mann–Whitney *U*-test, and differences in categorical variables were determined using Pearson's chi-square test. Ordered logistic regression analysis was used to explore associations with mMRC and exacerbation frequency. We evaluated the model adjusted for age, sex and $\%FEV_1$ as independent variables and mMRC ≥2 or number of exacerbations ≥2 within the past year as a dependent variable to determine the influence of gender differences on these dependent variables. The setting of independent variables was determined by referencing past literature within a feasible range for statistical processing. Associations were expressed as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was set to $p<0.05$. All statistical analyses were performed using JMP Pro version 16.1.0 (SAS Institute Inc., Cary, North Carolina, USA).

Results

A total of 1168 patients aged 40–95 years were recruited and analyzed in this study. Detailed results are presented in Table 1. Among the 1168 patients, 133 (11.4%) were female. A history of never smoking was significantly higher in females than males (13.5% vs 2.9%, $p<0.01$). The mean FVC and FEV_1 values in females were significantly lower than those in males (2.14 L vs 3.00 L, $p<0.0001$, and 1.15 L vs 1.59 L, $p<0.0001$, respectively). Although there was no difference in age (mean 72.1 vs 72.1, p=0.99) and $\%FEV_1$ (mean 60.5% vs 59.7%, p=0.65) or $FEV_1\%$ (mean 53.2% vs 52.3%, p=0.47) between females and males, mMRC and number of frequent exacerbators were significantly higher in females (mMRC≥2; 59.4% vs 47.2%, $p<0.01$, number of exacerbations≥2; 19.5% vs 11.8%, p=0.011) (Table 1 and Figures 1). Females were more likely to use long-term oxygen therapy (LTOT) and inhaled corticosteroids (ICS) (16.5% vs 9.8%, p=0.016, and 59.4% vs 41.4%, $p<0.0001$, respectively) than males. The prevalence of GOLD group B-D tended to be higher in females than in males (GOLD group B-D: 62.4% vs 49.9%, $p<0.01$) (Table 1). Adjusting for age and $\%FEV_1$ did not reduce the sex differences in mMRC and exacerbation frequency in ordered logistic regression analysis (mMRC: females versus males OR 2.02, 95% CI 1.32–3.09; p=0.0011, exacerbations: females versus males OR 2.04, 95% CI 1.25–3.33; p=0.0046). The results indicated that even after adjusting for the influence of age and airflow limitation, females exhibited significantly higher levels of dyspnea and exacerbation rates compared to males (Table 2).

Figure 2 shows the proportion of female patients in the CAP study cohort according to GOLD classification, defined by exacerbation history and mMRC. The percentages of female patients in groups A, B, C, D, and E were 8.8%, 12.6%, 12.9%, 18.8%, and 17.6%, respectively, in the 2017 or 2023 GOLD classifications. The relative ratios to GOLD group A were 1.43 in group B, 1.47 in group C, 2.14 in group D, and 2.00 in group E. The present study found an increased

Table 1 Patient Characteristics and Study Results

		Female (n=133)	Male (n=1035)	p value
Age		72.08 (±8.04)	72.09 (±8.36)	0.99
Smoking status	Never Former Current Former+current	18 (13.53%) 96 (72.28%) 19 (14.29%) 115 (86.47%)	30 (2.90%) 880 (85.02%) 125 (12.08%) 1005 (97.1%)	 <0.0001
mMRC, grade	0/1/2/3/4 ≥2	19/35/41/28/10 (14.29/26.32/30.83/21.05/7.52%) 79 (59.40%)	200/346/280/166/43 (19.32/33.43/27.05/16.04/4.15%) 489 (47.25%)	 <0.01
PFT	FVC (L) FEV_1 (L) FEV_1% (%) %FEV_1 (%)	2.14 (±0.68) 1.15 (±0.48) 53.15 (±11.07) 60.52 (±19.6)	3.00 (±0.8) 1.59 (±0.62) 52.32 (±12.23) 59.67 (±20.71)	<0.0001 <0.0001 0.47 0.65
Stage of GOLD	I/II/III/IV ≥II	21/66/40/6 (15.79/49.62/30.08/7.71%) 112 (84.21%)	190/497/264/84 (18.36/48.02/25.51/8.12%) 845 (81.64%)	 0.47
Group of GOLD 2017	A/B/C/D B-D	50/57/4/22 (37.59/42.86/3.01/16.54%) 83 (62.41%)	519/394/27/95 (50.14/38.07/2.61/9.18%) 516 (49.86%)	 <0.01
Exacerbation, year-1	0–1 ≥2	107 (80.45%) 26 (19.55%)	913 (88.21%) 122 (11.79%)	 0.011
LTOT Inhalation therapy	User ICS single LABA single LAMA single ICS+LABA LABA+LAMA ICS+LABA+LAMA ICS use No treatment	22 (16.54%) 1 (0.75%) 1 (0.75%) 26 (19.55%) 22 (16.54%) 26 (19.55%) 54 (40.60%) 79 (59.40%) 1 (0.75%)	101 (9.76%) 1 (0.10%) 71 (6.86%) 263 (25.41%) 152 (14.69%) 221 (21.35%) 268 (25.89%) 429 (41.45%) 51 (4.93%)	0.016 0.085 <0.01 0.14 0.57 0.63 <0.001 <0.0001 0.028

Notes: Data are presented as n (%) or mean ± SD. The FEV_1% was defined as the FEV_1/FVC ratio.
Abbreviations: PFT, pulmonary function test; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; %FEV_1, percent predicted forced expiratory volume in 1 s; LTOT, long-term oxygen therapy; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist.

proportion of female patients in more severe group (two times or more in groups D and E). In general, the COPD severity increased as the group advanced to A, B, C, or D (or E). It has been suggested that female patients are more affected by the disease than male patients in terms of subjective symptoms and the number of exacerbations.

Discussion

This study revealed several important clinical findings in female patients with COPD. Never-smokers accounted for one-eighth of the female patients with COPD and were not uncommon. Although age and degree of airflow limitation showed no disparity between the sexes, females exhibited smaller values of FVC and FEV_1 and greater severity of symptoms and exacerbation rates.

The prevalence of never-smokers among female patients with COPD in this study was significantly higher than that among male patients, at one in eight. Similar results have been reported in other countries.[1,5,6] Women are more vulnerable to tobacco smoke or biomass smoke from the cottage industry,[8,9] which explains why they develop COPD despite low exposure to smoking, a major cause of COPD. It is possible that the effects of exposure to smaller amounts of causative agents, such as short-term or low-intensity smoking at a young age, exposure to second-hand smoke from partners or co-workers even if the individual does not smoke, and exposure to other factors from living and working environments are relatively stronger than those in men and are linked to decreased lung function in female patients.

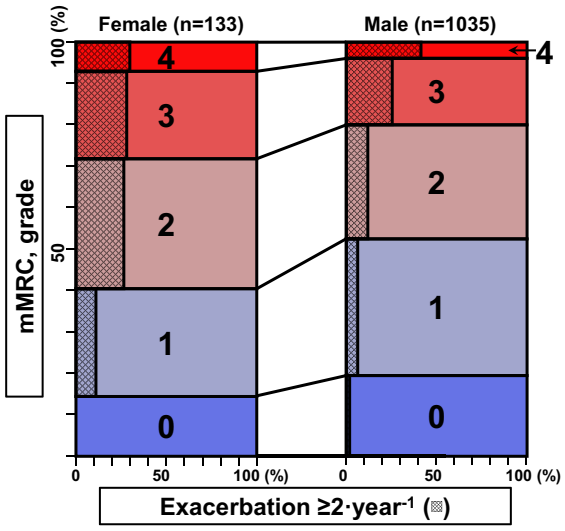

Figure 1 Proportion of each grade of mMRC and exacerbation frequency by sex. The exacerbation frequency was expressed as the percentage of instances where exacerbations occurred two or more times within the past year for each mMRC grade. Female patients were more likely to have a higher mMRC grade, and females exhibited higher exacerbation frequencies even at relatively lower mMRC grades, resulting in an overall higher observed rate of exacerbation events compared to males. mMRC, modified medical research council dyspnea scale.

Although this study did not collect data on secondhand smoking, the Japan National Health and Nutrition Survey Reports showed that secondhand smoking opportunities were more common among women than among men.[28] In Japan, indoor smoking was banned in all facilities as of April 2020.[29] Prevention of passive smoking may shed light on the future of COPD in women. Moreover, the stigma that COPD occurs in males especially smokers, may contribute to the under-diagnosis and delayed diagnosis of COPD in women. A recent study addressed the effect of the timing of COPD diagnosis on clinical outcomes.[30] Female patients with COPD are often undiagnosed and tend to experience delayed diagnosis compared to males.[31] Patients in the delayed diagnosis group had a higher risk of exacerbation and mortality compared to those who received an early diagnosis of COPD.[30] It is highly possible to make a diagnosis if proper pulmonary function tests are performed on the target women,[16] thus, barriers to spirometry should be lowered in female patients with unexplored respiratory symptoms, such as dyspnea, cough, or other suspicious medical or life histories. In addition, extrapulmonary factors such as grip strength and BMI may be associated with latent lung function decline in young adults,[32] and may be effective as convenient screening tests for COPD.

No sex differences were found in the age and degree of airflow limitation, although female COPD patients had smaller values of FVC and FEV_1, a higher frequency of exacerbations, stronger symptoms, and higher LTOT use. These results are consistent with those of previous studies. Although there are no sex differences in the severity of airflow

Table 2 Results of Logistic Regression Analysis in the Models Including Age, Sex and $\%FEV_1$ as Independent Variables and mMRC ≥2 or Number of Exacerbations ≥2 Within the Past Year as a Dependent Variable

	mMRC ≥2	p value	Exacerbation ≥2 year-1	p value
	OR (95% CI)		OR (95% CI)	
Age, per 1-year increase	1.05 (1.03–1.07)	<0.0001	1.00 (0.98–1.02)	0.98
%FEV1, per 1% increase	0.94 (0.94–0.95)	<0.0001	0.96 (0.95–0.97)	<0.0001
Sex (females versus males)	2.02 (1.32–3.09)	0.0011	2.04 (1.25–3.33)	0.0046

Notes: The results indicated that even after adjusting for age and $\%FEV_1$, females exhibited significantly higher levels of dyspnea and exacerbation rates compared to males.
Abbreviations: $\%FEV_1$, percent predicted forced expiratory volume in 1 s; mMRC, modified medical research council dyspnea scale; OR, odds ratio; CI, confidence interval.

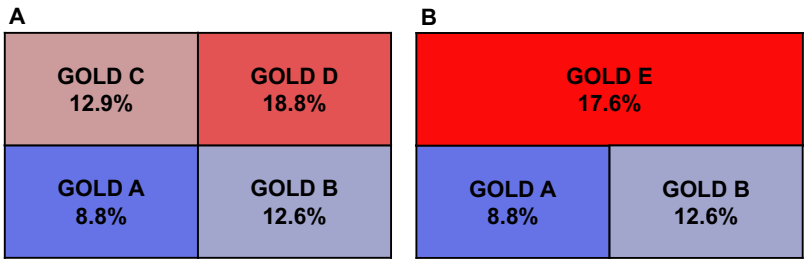

Figure 2 The percentage of female patients within each group of the GOLD ABCD classification (**A**) and ABE classification (**B**). The percentage of female patients was 11.4% in the overall cohort, 8.8% in group A, 12.6% in group B, 12.9% in group C, 18.8% in group D, and 17.6% in group E. The proportion of female patients increased in the more severe group. Female patients were more affected by the disease than male patients in terms of subjective symptoms and number of exacerbations.

limitation,[6,16] female patients with COPD tend to have a relatively high exacerbation frequency and proportion of severely ill patients.[1,5,16,17] They also have strong subjective symptoms of dyspnea[1,6,17] and a low QOL.[33] Considering the high use of LTOT and opioids in female COPD,[17,34] management focusing on palliative care will become more important.

In general population considerations, it has been reported that the difference in symptoms of dyspnea may be attributed to the disparity in absolute values of FEV_1 and FVC.[35] It is widely believed that individuals with smaller lung capacities and narrower airways (which is often the case for females but also applies to smaller-built males) experience more intense respiratory effort during physical exertion. This phenomenon is attributed to the utilization of a higher proportion of ventilatory capacity and the subsequent increase in respiratory resistance.[35] Increased respiratory effort enhances the neural respiratory drive and is perceived as an increase in the intensity of breathlessness.[36] Although there are no similar studies focusing on COPD, in this study, the mean FVC and FEV_1 values in females were significantly smaller at approximately 70% of those in males. This difference might be one of the reasons for the stronger subjective symptoms in females; however, further research targeting COPD patients is necessary.

Female patients with COPD frequently have asthma-like conditions, as well as bronchiectasis, depression, anxiety, metabolic syndrome, and osteoporosis.[1,6,16,17] These comorbidities may also influence the intensity of subjective symptoms. However, the CAP study did not accurately assess comorbidities; therefore, the impact of comorbidities could not be examined. Patients with other pulmonary diseases were established as exclusion criteria, but may not have been completely ruled out. There have been reports of underdiagnosis of asthma and bronchiectasis in patients with COPD.[37,38] This study showed a higher prevalence of ICS use among women, suggesting an underlying asthma-like condition. Although there is a lack of information regarding sex differences in ICS treatment in patients with COPD, some previous reports indicate that the frequency of ICS use was similar between men and women[6,33] or higher in men,[5] which differs from the results of this study. The use of ICS in COPD may be considered from the perspective of exacerbation prevention.[24,39] The higher rates of exacerbations in women may also have contributed to making ICS a more favorable choice for exacerbation prevention.

Some reports suggest that women have more pulmonary embolisms and poor adherence as causes of COPD exacerbation.[5] Inappropriate high-dose corticosteroid use is a risk factor for pulmonary embolism and infection and is considered a risk factor for the exacerbation of COPD. An exacerbation event is a serious pathological condition that greatly reduces lung function in COPD, and understanding the differences in the characteristics of men is very important for exacerbation prevention. It is also presumed to be related to other complications such as osteoporosis. Systemic corticosteroid administration and ICS are known risk factors for osteoporotic fractures, especially in women.[40] The use of corticosteroids should be strictly considered and restricted to the lowest required doses. This was a cross-sectional study in which we did not evaluate comorbidities including pulmonary embolism, infection, and osteoporosis; therefore, future studies are warranted.

Our study has several limitations. First, this was a retrospective study that used a cohort from previous studies. Thus, it may not reflect the latest treatments. Second, the data collected were limited. Critical body mass indices such as BMI and laboratory data, including blood gases, were not collected. Patients with respiratory comorbidities were excluded,

and information on other comorbidities was not collected. Further studies are required from this perspective. Third, since the diagnosis was left to the attending physician, it is possible that the patients' backgrounds varied (ie, an inappropriate diagnosis was made). In fact, the frequency of ICS utilization among women is greater than that commonly reported, and there is a possibility that certain patients with asthma were also included. Finally, we used cohorts from a limited region and the clinical characteristics may differ from those in other regions.

Conclusion

Management reality revealed that many challenges remain in overcoming the high disease burden of female COPD patients in Japan. Physicians should be aware that female without a smoking history may also develop COPD and should consider treatment interventions focused on the typical characteristics of female COPD, such as lower lung capacity, respiratory failure, and asthma-like conditions.

Disclosure

Prof. Dr. Tomoyuki Kakugawa is an employee of the Department of Pulmonology and Gerontology, Graduate School of Medicine, Yamaguchi University, Ube, Japan, which is funded by the Medical Corporation, WADOKAI. The authors report no other conflicts of interest in this work.

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