Review Article on Current Epidemiology and Policies of COPD Worldwide

Narrative review of current COPD status in Japan

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Abstract: Chronic obstructive pulmonary disease (COPD) causes morbidity and mortality worldwide. Due to the improvement in environmental sanitation and medical care, the general life span has increased in the past decades in Japan. However, many older patients with COPD develop a wide range of comorbidities, and the impairments in the activities of daily living result in frailty and increase social and economic burdens. Population-based studies have shown that the prevalence of COPD is approximately 10% among subjects aged ≥40 years, but more than 80% of COPD patients are underdiagnosed. The Ministry of Health, Labour, and Welfare in Japan proposed the National Health Promotion in the 21st century, termed Health Japan 21 (the second term), in 2013 to prevent the onset and progression of noncommunicable diseases (NCDs), including COPD. The government, medical society, and community have been attempting to increase the recognition of COPD and promote smoking cessation. Additionally, Japanese cohorts have revealed distinct clinical features in Japanese patients with COPD, including lower rates of patient-reported exacerbations, less frequent coexisting cardiovascular disease and metabolic syndrome, and lower use of inhaled corticosteroids in Japan compared to the Western countries. Moreover, the poor adherence to inhaled medications is found in approximately 20% of subjects, and rehabilitation is performed in 26% of hospitalized patients with COPD. Therefore, more efforts should be made to improve adherence and access to pulmonary rehabilitation. Overall, Japanese COPD patients share common clinical and social features with COPD patients in other countries. Further international corroboration may help establish better comprehensive management of the disease.

Keywords: Chronic obstructive pulmonary disease (COPD); emphysema; Japan; prevalence

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major respiratory disease that is characterized by respiratory symptoms and airflow limitation. While COPD is considered preventable and treatable, it is a leading cause of death worldwide and imposes large social and economic burdens, especially in ageing societies. Excess health-care resource utilization, increased medical costs, and loss of productivity are also social problems. Based on the current situation, this review aimed to summarize the prevalence and underdiagnosis of COPD, government policies, clinical features distinct from those of other countries, adherence to inhaler therapy, and availability of pulmonary rehabilitation in Japan. We present the following article in accordance with the Narrative Review Reporting Checklist (available at https://dx.doi.org/10.21037/jtd-20-2263).

Table 1 Summary of the prevalence and underdiagnosis of COPD in Japan

Study	Year	Participants	N	Prevalence	Underdiagnosis
NICE (2)	2000	Age ≥40	2,343	10.9%	80.6%
		Male age ≥40		16.4%	–
		Female age ≥40		5.0%	–
		Male smokers age ≥40		17.1%	–
		Female smokers age ≥40		7.5%	–
		Age 40–49		3.5%	–
		Age >70		24.4%	–
Takahata (3)	2004–2005	Age ≥40	2,917	10.6%	–
		Male age ≥40	1,325	16.2%	–
		Female age ≥40	1,592	5.8%	–
Hisayama (4,5)	2008	Age ≥40	2,100	11.3%	–
	1967	Male age ≥40	824	26.3%	–
		Female age ≥40	1,018	19.8%	–
	2012	Male age ≥40	1,340	16.1%	–
		Female age ≥40	1,693	10.5%	–
Nagahama (6)		Age 30–74	9,040	3.8%	–
Medical checkup (7)	2012–2013	Age ≥40	22,293	4.3%	–
		Smokers age ≥40	10,981	6.1%	80.6
		Smokers age 40–49	3,745	2.2%	–
		Smokers age 50–59	4,031	4.4%	–
		Smokers age ≥60	3,194	12.8%	–
Cardiovascular clinic (8)	–	Smokers with cardiovascular disease, age ≥40	995	27.7%	87.7%

NICE (2), Takahata (3), Hisayama (4,5), and Nagahama (6) studies were conducted with a population-based approach. "Medical check-up" indicates a study that recruited subjects who underwent comprehensive medical examination, including spirometry (7). "Cardiovascular clinic" indicates a study that recruited outpatients with cardiovascular disease at primary care clinics and performed spirometry (8).

Prevalence of airflow limitation and underdiagnosis of COPD

The prevalence of airflow limitation and/or COPD is affected by multiple factors, such as region, definition of COPD, age, ethnicity, and smoking habit. A systematic review and meta-analysis showed that the global prevalence of physiologically diagnosed COPD was 9–10% among subjects aged 40 years or older (1). The prevalence of airflow limitation and the underdiagnosis of COPD according to population-based cohorts and clinic/hospital-based cohorts in Japan is summarized in *Table 1* and compared to the global data in *Figure 1*. In 2000, a population-based study in Japan, called the Nippon COPD Epidemiology (NICE) study showed that the prevalence of airflow limitation (FEV_1/FVC <0.7 without bronchodilators) in 2,343 Japanese subjects aged ≥40 years was 10.9% (16.4% among males and 5.0% among females) (2). The prevalence in former and current smokers was 15.6% and 15.4% whereas 5.8% of lifelong non-smoker showed the airflow limitation. These suggest that long-term exposure to cigarette smoke is a main cause of COPD in Japan, but other multiple factors such as abnormal lung growth, a prior history of asthma, and aging might be associated with the airflow limitation. Notably, a prior diagnosis of COPD was made in only 9.4% of those with airflow limitation.

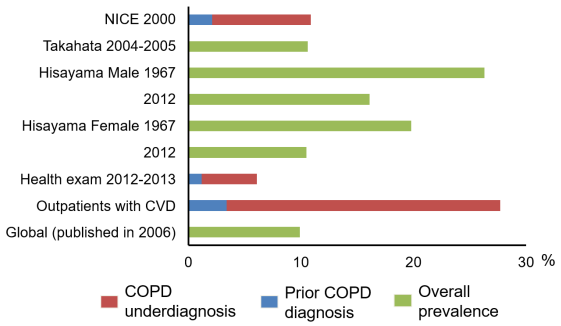

Figure 1 Prevalence and underdiagnosis of COPD in Japan. All data were based on subjects aged ≥40 years. NICE (2), Takahata (3), and Hisayama (5) were conducted with a population-based approach. "Health exam" indicates a study of subjects who underwent comprehensive medical examination including spirometry (7). "Outpatients with CVD" indicates a study of outpatients with cardiovascular disease (CVD) at primary care clinics and performed spirometry (8). "Global data" indicates a meta-analysis of 34 studies including subjects aged ≥40 years (1).

This finding was reproduced in other population-based studies that showed that the prevalence of airflow limitation based on FEV_1/FVC <0.7 without bronchodilators was 10.6% (Takahata study, n=917) and 11.3% (Hisayama study, n=2,100) among subjects aged 40 years or older (3,4). In the population-based Nagahama study that enrolled subjects aged 30 to 74 years old, the prevalence of COPD (defined as FEV_1/FVC <0.7 without bronchodilators) was 3.8%, which is lower than that in the studies of subjects aged 40 years or older (6). More recently, the prevalence of airflow limitation in 1967 was compared to that in 2012 using two serial population-based Hisayama cohorts (5). The prevalence decreased from 26.3% to 16.1% in men and 19.8% to 10.5% in women. Those authors suggested that the reduction in the prevalence of airflow limitation can be attributed to the improvement in environmental pollution in the atmosphere and workplace, as well as the lower smoking rate.

Studies have also shown the prevalence of airflow limitation in specific populations. In 995 patients aged ≥40 years who had a smoking history of ≥10 pack-years and were treated for cardiovascular disease at 17 medical centres in Japan, the prevalence of airflow limitation (FEV_1/FEV_6 <0.73 without bronchodilators) was 27%, and 87.7% of those patients had not previously been diagnosed with COPD (8). Additionally, in smokers aged ≥40 years who underwent comprehensive medical examinations, the prevalence of airflow limitation (FEV_1/FVC <0.7 without bronchodilators) was 6.1%, and 80.6% had not been previously diagnosed with COPD/emphysema (7). Moreover, a combination of the International Primary Care Airways Group (IPAG) Questionnaire and spirometry showed that the prevalence of COPD (defined as FEV_1/FVC <0.7 without bronchodilators) was 29% in former and current smokers aged 50 to 74 years old and 37% in those aged 75 years old or more in Ohmuta city in Japan, an area with high levels of air pollution (9). In that study, even 16% of non-smokers aged 50 years or more showed spirometric evidence of COPD. These results suggest that while the overall prevalence of COPD in the general population aged ≥40 years is approximately 10% in Japan, the prevalence may increase up to 30–40% in smokers with cardiovascular disease and those who lived in areas with high air pollution.

Government policies

Due to improvements in environmental sanitation and medical care, the life span has increased in the past decades, but during the same period, morbidity due to noncommunicable diseases (NCDs) has imposed increasing substantial social burdens. The Japanese government proposed the National Health Promotion in the 21st century, termed "Health Japan 21 (the first term)", in 2000 to prevent the occurrence of major NCDs, including cancer, heart disease, stroke, and diabetes (10). Moreover, the Japanese government enacted the Health Promotion Law to prevent non-smokers from being exposed to cigarette smoke in public facilities in 2003 and allowed for coverage of the smoking cessation programme in the Japanese medical insurance system in 2006.

COPD was not included in the Heath Japan 21 (the first term). However, the number of subjects who died from COPD has increased continuously (*Figure 2*), and many older patients with COPD develop a wide spectrum of comorbidities. The impairment in activities of daily living results in frailty and has been recognized as a social problem (11). In 2013, the Ministry of Health, Labour, and Welfare in Japan revised the Health Japan 21 (the second term) and added COPD to the list of target NCDs (12). One of the goals in the Health Japan 21 is to prevent the incidence and progression of NCDs, including cancer, cardiovascular disease, diabetes mellitus, and COPD. Specifically, the government is attempting to increase the recognition of COPD from 25% of the generation population in 2011 to 80% by 2022 and to promote further

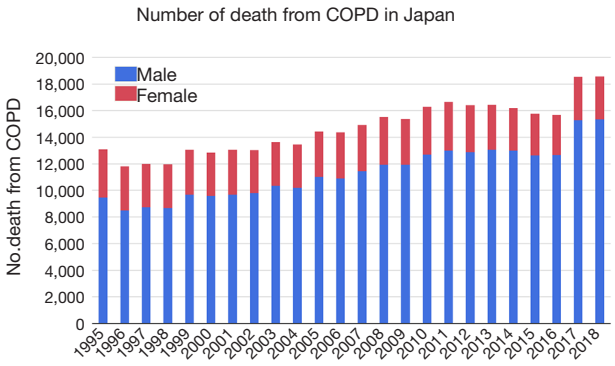

Figure 2 Trend in number of deaths from COPD in Japan. Data were obtained from the nationwide database of the Ministry of Health, Labour, and Welfare in Japan.

smoking cessation to prevent COPD. Unfortunately, the current awareness of COPD is still around 30% (13).

Distinct clinical features in Japanese COPD patients

A diagnosis of COPD is based simply on airflow limitation that is induced by a combination of airway disease and emphysema. The relative contributions of the two structural abnormalities vary from person to person, and the clinical manifestation of the disease is substantially heterogeneous. In a nationwide survey, CT data from 1,438 patients with COPD (FEV_1/FVC <0.7 without bronchodilators) were evaluated. Consequently, 90% had emphysema-dominant COPD and only 10% had airway-disease-dominant COPD (14). Meanwhile, in a multicentre study conducted across five European countries, there were 124 CT-based emphysema-dominant and 79 airway-disease-dominant phenotypes among 441 patients with COPD (15). In the COPDgene study conducted in the United States (n=4,187 and 4,101 for training and validation datasets, respectively), cluster analysis identified an airway-disease-dominant disease phenotype in 24% of smokers and a severe emphysema-dominant phenotype in 20% of smokers (16). These suggest that the relatively lower rate of airway-disease-dominant COPD and higher rate of emphysema-dominant COPD may be a feature of Japanese COPD studies although whether this reported value actually reflects the real prevalence of airway-disease-dominant COPD is unclear.

Another distinct feature of Japanese COPD is that patient-reported exacerbation rates are lower than those in other countries (17). In the UPLIFT trial that examined the effects of tiotropium in 30 countries, including Japan, the exacerbation rate in Japanese patients (0.61/person/year) was lower than that in patients from other Asian countries (0.92/person/year) and all countries (0.85/person/year). This difference was reflected by the 2017 GOLD ABCD classification in Japan and Spain and the United States, where groups C and D were less common in Japan than in Spain and the United States (18,19). Although the definite reasons for the different rates of exacerbations in Japan and other countries remain unclear, better medical access, less frequent cardiovascular comorbidity, and better adherence to inhaled medications as described below might contribute to less frequency of exacerbations in Japan (17,20). Additionally, as described in a previous review, there is the hypothesis that Japanese patients with COPD may tend to underreport their symptoms, which causes less frequency of reported exacerbations (17).

Moreover, the comorbidities of COPD are affected by multiple factors and vary among regions. In a review summarizing comorbidities in Japanese patients with COPD, cardiovascular disease and metabolic syndrome are less frequent and osteoporosis, lower body mass index (BMI), and malnutrition are more frequent in Japanese patients with COPD than in Westerners with COPD (20-22). The prevalence of osteoporosis was 18-39% and 9% in Japanese and Hungarian patients with COPD, respectively and the prevalence of diabetes was 7.8% in Japanese subjects with airflow limitation (FEV_1/FVC <0.7 without bronchodilators) and 12% in Hungarian patients with COPD (20,22-24). These differences could be explained by genetic backgrounds and social and dietary behaviours. Nonetheless, we should also be aware that the prevalence of comorbidities may change in different samples. As shown in *Figure 3*, in observational studies conducted in a hospital, a cardiovascular disease accounts for approximately 12% of deaths in Japanese patients with COPD (diagnosed based on post-bronchodilator FEV1/FVC <0.7) (25,26). In contrast, a cardiovascular disease accounted for approximately 30% of all-cause deaths in the IMPACT study conducted worldwide (28). However, in a population-based study in Takahata, of 3,253 Japanese subjects enrolled, 338 showed airflow limitation without apparent respiratory symptoms (27). Notably, 31 patients with airflow limitation died during a 7-year follow-up, and the causes of death were respiratory failure (32%), cardiovascular disease (29%), lung cancer (16%), and other organ neoplasms (13%) (27). In terms of the annual rate of deaths related to COPD, the Takahata study suggests

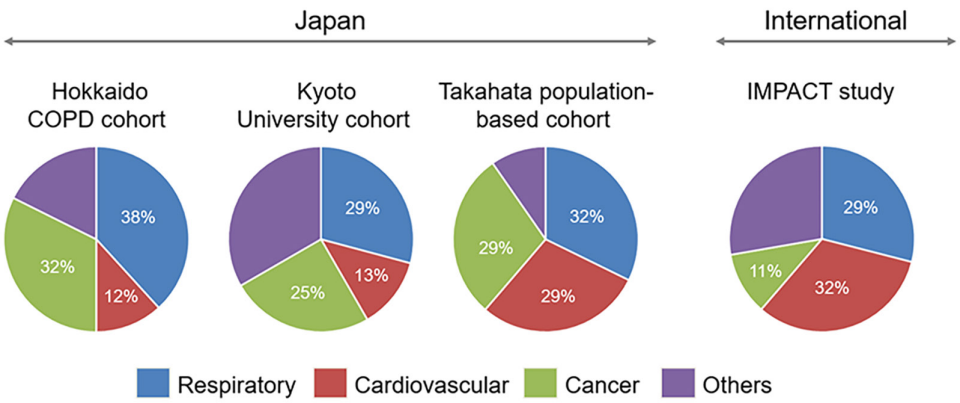

Figure 3 Causes of death in patients with COPD from Japanese and international studies. The Hokkaido COPD cohort (25) and Kyoto University cohort (26) were conducted at hospitals, and forced expiratory volume in 1 sec (FEV1) was approximately 60% (% predicted). The Takahata study (27) was a population-based study in which subjects with airflow limitation were included, but the severity of airflow limitation was mild (mean FEV1 was over 90% of predicted). IMPACT (28) was an international multicentre interventional study conducted in the United States, Europe, and Asia.

that the annual rate of death in patients with COPD should be 1–2%. Therefore, assuming that there are at least 6 million COPD patients in Japan, the number of annual deaths related to COPD would be approximately 60,000. However, this calculated number is more than the reported number (18,000) as shown in *Figure 2*. This discrepancy could be because underdiagnosis of COPD might have affected the number of reported deaths associated with COPD.

Asthmatic features in COPD

Longitudinal studies have confirmed that a history of asthma including childhood asthma increases a risk of COPD (29). Moreover, COPD patients with a history of asthma have higher risk of exacerbations and respond to inhaled corticosteroid (ICS) (30). In the Kyoto-Himeji cohort which prospectively enrolled 189 Japanese patients with COPD, a history of asthma before age of 40 years was found in 28% of those with CT-defined airway disease-dominant COPD and 6% of those with CT-defined emphysema disease-dominant COPD (31). This suggests that a prior history of asthma could be associated with the development of airway disease-dominant COPD. Moreover, the Japanese Respiratory Society (JRS) proposed the diagnostic criteria of asthma-COPD overlap (ACO) in 2018, conducted a multicentre study including 708 patients with COPD, and found that 255 (36%) had a physician's diagnosis of asthma (32). Furthermore, of 396 whose data are sufficient to evaluate the new ACO criteria, 25.5% fulfilled the criteria of ACO (32). Meanwhile, in the Hokkaido COPD cohort (n=268), 21% patients had bronchodilator reversibility, 19% had blood eosinophilia, and 25% had atopy even though patients with a history of asthma were not included (33). In the Western countries, the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) showed the percentage of COPD patients with a past history of asthma was approximately 20% (34), and the COPD History Assessment in Spain (CHAIN) cohort including 831 patients with COPD showed that 15% met the criteria of ACO (35). Therefore, there seems to be no large difference in the prevalence of a history of asthma and/or asthmatic features in patients with COPD between Japan and other countries.

Adherence to inhaled medications

Appropriate adherence to inhaled long-acting bronchodilators and ICS is essential for the management of COPD. Poor adherence leads to the increased risk of poor clinical outcome, such as reduced quality of life and increased health-care expenditures (36). A Japanese multicentre cross-sectional study analysed adherence in 479 consecutive outpatients with asthma and/or COPD who were taking both regular inhaled and oral medication (37).

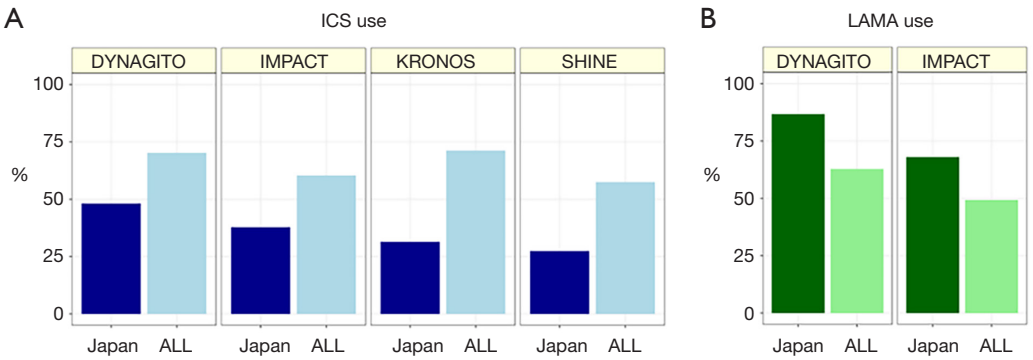

Figure 4 Use of ICSs and LAMAs prior to enrolment in international interventional studies. DYNAGITO (41,42), IMACT (43,44), KRONOS (45,46), and SHINE (47,48) studies were conducted all over the world, including in the United States, Europe, Asia, and Japan. The use of inhaled corticosteroids (ICSs) and long-acting muscarinic antagonists (LAMAs) was compared between a subset of the Japanese population and the whole data set.

Of 124 patients with COPD, 21.8% showed poor adherence to inhaled medication, and 9.7% showed poor adherence to oral medication. In another Japanese cohort, adherence to inhaled medication among COPD patients in different age groups was analysed (38). While COPD patients aged 75–84 years old (n=115) had more dyspnoea, lower exercise tolerance, poorer activity of daily living, more frequent severe exacerbation, and greater cognitive decline than those aged 65–74 years old (n=101), adherence to inhaled medications did not differ between the groups (good adherence rate =82% for 65–74 years of age and 89% for 75–84 years of age). The percentage of patients with good adherence in Japan is higher than that in 34.7% in South Korea and 37.4% in Vietnam (39,40).

The use of ICSs and long-acting muscarinic antagonists (LAMAs) to treat COPD appears to be different from that in other countries. We assessed the use of these inhalers among individuals prior to enrolment in pharmaceutical interventional studies that were conducted worldwide, including the United States, Europe, and Asia. *Figure 4* compares the uses of ICS-containing (A) and LAMA-containing (B) regimens in a subgroup analysis of Japanese COPD patients to those in the complete datasets of COPD patients worldwide (41-48). ICS use was less frequent, and LAMA use was more frequent in Japan. This might be partially influenced by the current guideline from the Japanese Respiratory Society, in which long-acting bronchodilators, but not ICS, are main therapeutic agents in COPD while ICS should be used only in patients with asthmatic features (49).

Pulmonary rehabilitation

Pulmonary rehabilitation has been shown to be effective in improving exercise capacity, health-related quality of life, physical activity, and mortality (50-52). Thus, patients with greater symptoms and lower ability to perform activities of daily living should be referred to rehabilitation programmes, and health-care workers and society need to make the rehabilitation programme more accessible and affordable. However, pulmonary rehabilitation has not been implemented as widely as pharmacological intervention. In 18,037 hospitalized patients with COPD from the Japanese Diagnosis Procedure Combination nationwide administrative claims database, only 25.5% underwent rehabilitation (50). Pulmonary rehabilitation for outpatients is significantly less frequently performed compared to rehabilitation for other non-pulmonary diseases, such as locomotive diseases. Improvement in the environment to implement pulmonary rehabilitation for outpatients is required.

Long-term oxygen therapy (LTOT)

In the COPD Assessment in Practice (CAP) study, 123 out of 1,168 Japanese patients with COPD (10%) received LTOT (18). Another report showed that the percentage of COPD patients using home-based LTOT to all patients using home based LTOT has been approximately 50% over time (53). In a single center prospective study, of 101 COPD patients who showed mild hypoxaemia (PaO_2<80 Torr) at the baseline evaluation, 10 (10%) developed

chronic respiratory failure during 6-year follow-up and started LTOT. Diffusion capacity for carbon monoxide (D_{LCO}) at the baseline was associated with higher risk of future administration of LTOT in patients with COPD (54).

Bronchoscopic lung volume reduction

Bronchoscopic lung volume reduction (BLVR), particularly using endobronchial valves, has been shown to be effective in improving lung hyperinflation and exercise capacity in COPD patients (55). However, although a phase III trial had been conducted, the use of this procedure is limited in Japan. In a small report, BLVR using transbronchial infusion of autologous blood and thrombin was effective in 3 patients with very severe COPD (56). This concept needs to be further investigated in Japanese patients with advanced emphysema.

Conclusion

The prevalence rates of airflow limitation and COPD underdiagnosis are still high in Japan. Distinct clinical features such as high frequency of osteoporosis, low BMI, malnutrition, lower frequency of reported exacerbations and less frequently use of ICS in Japan should be considered when interpreting results and guidelines made based on international studies.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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