Systematic Review

The Economic Burden of Chronic Obstructive Pulmonary Disease in the Asia-Pacific Region: A Systematic Review

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a significant and disabling condition that entails high economic burden for society. **Objective:** The aim of this article is to assess cost studies of COPD and analyze cross-country cost comparisons in Asia-Pacific. **Methods:** A systematic literature search from October 2000 to October 2018 was conducted using PubMed, MEDLINE, and EMBASE to identify relevant studies. Costs reported by the different studies were converted to 2017 US dollars using the consumer price index for medical care. The quality of the studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards. **Results:** Ten studies (6 countries and 11 estimates) were identified and included for full review after consideration of the inclusion and exclusion criteria. Annual total societal costs of COPD ranged from $4398 to $23 049 per capita in Japan and $453 to $12 167 in South Korea. There were no intracountry comparison estimates for the remaining countries

(Singapore: $2700; Taiwan: $4000; China: $3942; and Thailand: $1105). In addition, there were estimates of partial costs in Singapore and Taiwan. **Conclusions:** Results of this review showed high cost variations between countries, with estimates in 2 countries (Japan and South Korea) exceeding those in UK and USA. Wide variation in disease cost estimates will continue to exist as long as there are differences in cost methodologies, disease severities included, and data limitation. We propose that researchers conducting burden-of-illness studies use standard methods and reporting formats to support cross-country comparisons.

Keywords: Asia-Pacific, chronic obstructive pulmonary disease, direct costs, indirect costs, societal costs.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a global health concern. It is a leading cause of morbidity and mortality worldwide. By 2030 it is predicted to become the third leading cause of death and the sixth cause of disability worldwide.[1] COPD results in a high economic burden that includes both direct costs of healthcare resource utilization and indirect costs of lost productivity.[2,3] The burden of a disease is estimated from data on prevalence, mortality, and healthcare utilization.[4,5] COPD imparts a significant disease burden in Asia-Pacific. This systematic review covered 6 countries in Asia-Pacific (South Korea, Japan, China, Taiwan, Singapore, and Thailand). Australia and New Zealand were included in the search strategy; nevertheless, both were excluded in the estimates because they did not meet the criteria for inclusion. The prevalence rate of COPD in Asia-Pacific was 6.2%,[6] almost on par with 6.7% in the United States.[7] Across the

region, prevalence rates ranged from a low of 5.3% in Thailand,[6] 5.9% in Singapore,[6] 6.1% in Taiwan,[8] 7% in Japan, and 8.2% in South Korea[7] to a high of 13.6% in China.[9] COPD weighted-average mortality rates (per 10 000) for people at least aged 40 years (1991-2004) varied from 3.0 (South Korea) to 4.6 (Taiwan).[4]

The economic burden of direct costs for respiratory diseases is greater in countries with lower wages[10] (India 28% of average wages, Korea 4%, and Singapore 2%). Nevertheless, there was less variation in societal costs of respiratory diseases among countries[10] (39%-71% of average wages). This might be due to lost work productivity rather than direct healthcare costs, the biggest contributor to overall costs for illnesses. Low direct costs in countries such as Singapore (where government subsidizes partial medication costs in public clinics) may be offset by high indirect costs (labor costs or paid helpers), whereas countries such as Thailand may have high direct costs (medication costs) but relatively low indirect costs (eg, informal care by family members).
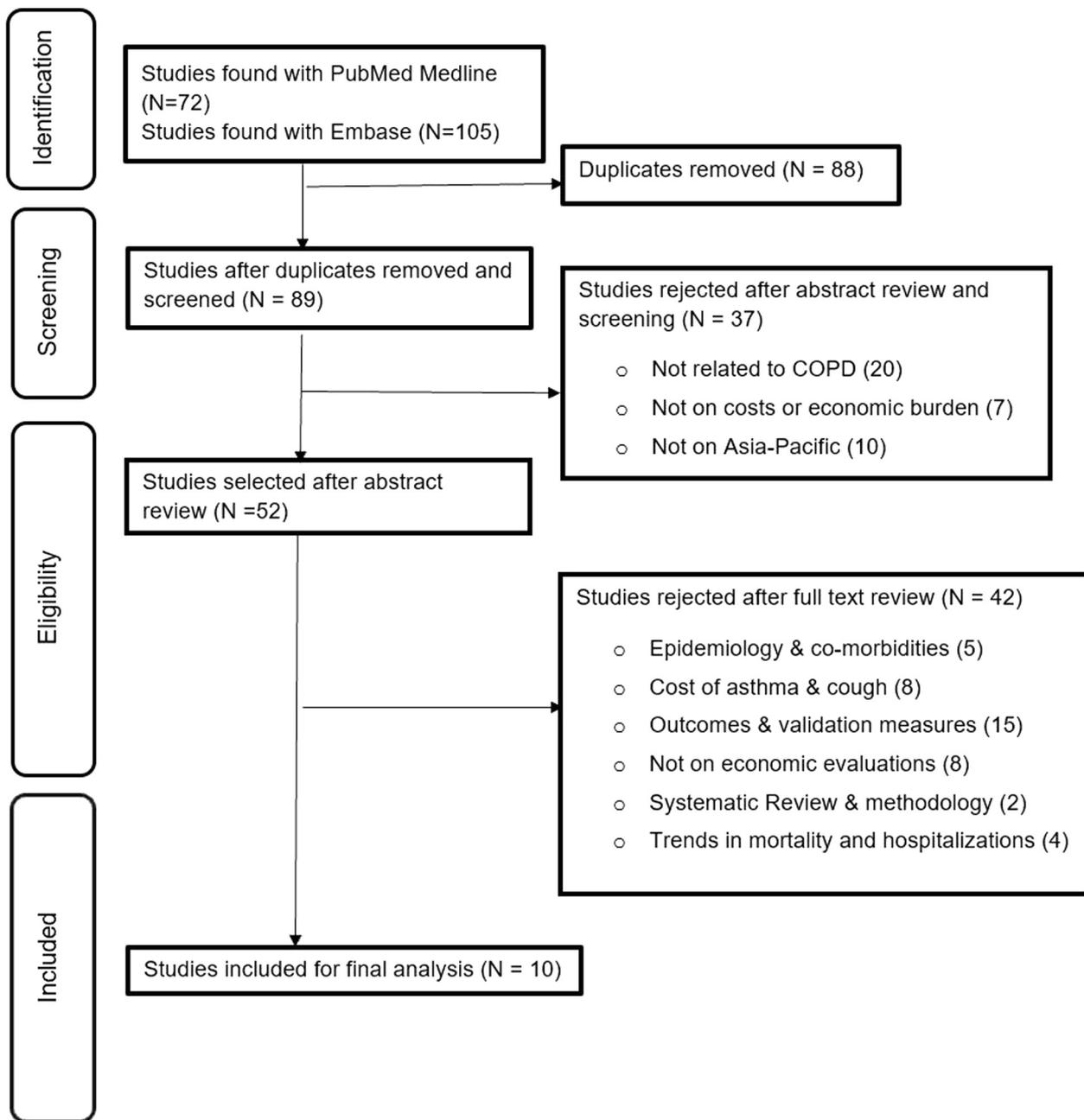
Fig. 1 – Flow diagram of the selection process of studies for the systematic review, in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. COPD indicates chronic obstructive pulmonary disease.

The aim of this article is to review publications on COPD in Asia-Pacific countries with specific reference to cross-country societal cost comparisons by examining study design, costing methods, and analytic perspectives.

Methods

A systematic literature search was carried out through a comprehensive search of databases in Excerpta Medica Database (EMBASE) and PubMed Medical Literature Analysis and Retrieval System Online (MEDLINE) from October 1, 2000, to October 1, 2018. This systematic review was conducted in accordance with the

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[11]

Primary Outcome: The Economic Cost of Chronic Pulmonary Disease

The primary purpose of this review was to determine the cost of COPD in Asia-Pacific. The study investigated direct costs (inpatient & outpatient hospitalization visits, medications, and comorbidities), indirect costs (productivity loss), methods (cost of illness, weighted attribution), and approaches (prevalence, incidence) related to COPD.

Table 1 – Summary of cost studies in the review.						
Author (year), reference, countries	Study design	Type of costs	Cost perspective	Cost method	Cost approach	Main findings
Foo et al (2016),[15] Japan, South Korea	Prospective: Cross-sectional population-based survey on direct and indirect costs. 4343 participants aged 40 years and older with mild, moderate, and severe COPD from 2012 to 2013. Direct costs were based on those requiring emergency departments, outpatient and inpatient services, home oxygen therapy, medication and comorbidity. Indirect costs were from work loss and premature mortality.	Total	Societal	Cost of illness	Prevalence based	The annual societal cost per capita was US$ 13 829.40 for Japan and US$ 8324.50 for South Korea (2013). Indirect costs contributed 53% and direct costs 47% in Japan, whereas in South Korea, indirect cost was 92% and direct cost was 8%.
Teo et al (2012),[17] Singapore	Prospective: Analysis of hospitalization episodes and comorbidities from public databases. 5125 participants aged 40 years and over from 2005 to 2009. Direct costs were from utilization of health services in inpatient and outpatient, emergency department, and comorbidity.	Direct	Healthcare provider	Weighted attribution	Prevalence based	The annual direct cost of 2 healthcare clusters in Singapore was $11 million (2009), with inpatients hospitalization contributing 68% and 32% from emergency, specialist outpatient and primary care visits. The annual direct cost per capita was $2280.
Wang et al (2016),[10] Singapore (APBORD study)	Prospective: Cross analysis of direct and indirect costs of 5250 participants ≥18 years at 22 study sites for 1 year from 2012 to 2013. Direct costs included visits to inpatient/outpatient services, emergency, medication, and comorbidity. Indirect costs included loss in income from participants (absenteeism) and loss of productivity while working (presenteeism)	Total	Societal	Cost of illness	Prevalence based	The annual total societal cost per capita was $4500 (60% indirect and 40% direct costs).

Table 1 – *continued*

Author (year), reference, countries	Study design	Type of costs	Cost perspective	Cost method	Cost approach	Main findings
Nishimura and Zaher (2004),[14] Japan	Prospective: Analysis of direct and indirect costs by building a deterministic model using publicly available data from 1990 to 2002. Moderate to high severity of COPD participants 40 years and over. Direct costs consist of inpatient and outpatient care, and home oxygen therapy. Indirect costs consist of number of missed days.	Total	Societal	Cost of illness	Prevalence based	The annual societal cost per capita was $3694 for Japan in 2000, with 80% of direct costs and 20% of indirect costs.
Kim et al (2016),[16] South Korea	Retrospective: Analysis of direct and indirect costs using government and public institutions databases from 2004 to 2013. Ten-year mean number of 1 264 140 participants with no age limit with moderate and severe COPD. Direct costs consisted inpatient/ outpatient services and medication. Indirect costs consisted of productivity loss due to missed day's worked and premature mortality.	Total	Societal	Cost of illness	Prevalence based	The annual societal cost of COPD was $439.9 million (2013), with 41.4% of indirect costs and 58.6% of direct costs. The annual societal cost per capita was $309.8.
Yoo et al (2016),[20] South Korea (APBORD study)	Prospective: Cross-sectional analysis of direct and indirect costs of 999 participants ≥18 years at 8 study sites for 1 year from 2012 to 2013. Same direct and indirect costs components as Wang et al's[10] study.	Total	Societal	Cost of illness	Prevalence based	The annual total societal cost per capita was $7900 (77% indirect and 23% direct costs).
Lin et al (2016),[19] Taiwan (APBORD study)	Prospective: Cross-sectional analysis of direct and indirect costs of 1001 participants ≥18 years at 8 study sites for 1 year from 2012 to 2013. Same direct and indirect costs components as Wang et al's[10] study.	Total	Societal	Cost of illness	Prevalence based	The annual total societal cost per capita was $8000 (71% indirect and 29% direct costs).

Table 1 – continued						
Author (year), reference, countries	Study design	Type of costs	Cost perspective	Cost method	Cost approach	Main findings
Chiang (2008),[18] Taiwan	Prospective: Analysis of hospitalization episodes from medical records. 160 participants aged 40 years and over for 1 year from 2002 to 2003. Direct costs were from annual utilization of health services in inpatient and outpatient clinic visits and emergency department.	Direct	Societal	Cost of illness	Prevalence based	The mean total direct costs per capita were $1092, $4258, and $8252 for moderate A, moderate B, and severe COPD participants, respectively.
Fang et al (2018),[9] China	Prospective: Analysis of prevalence rates across 7 major regions in China. 66 752 Chinese citizens aged 40 years and above over 1 year (2014-2015) with mild, moderate, and severe COPD	Total	Societal	Cost of illness	Prevalence based	Annual total cost of COPD ranged from $1964 to $3449 per capita (2014-2015). Prevalence rate was 13.6% (using postbronchodilator test).
Thanavirantananich et al (2016),[21] Thailand (APBORD study)	Prospective: Analysis of direct and indirect costs of 1995 participants ≥18 years at 4 study sites for 1 year from 2012 to 2013. Same direct and indirect costs components as Wang et al's[10] study.	Total	Societal	Cost of illness	Prevalence based	Annual total societal cost of COPD was $3000 per capita (2013), with $750 (25%) indirect and $2250 (75%) direct costs.

Search Strategy

For both MEDLINE and EMBASE database library studies, the MeSH and EMTREE terms "Bronchitis, Chronic/ or pulmonary disease," "Asia-pacific," and "Direct Service Costs/ or cost of illness/ or healthcare costs/ or health expenditures" were combined with keywords "chronic bronchitis or COPD," and "systematic review or methodology or economic burden." The search criteria were (1) English language, (2) human participants, (3) October 1, 2000, to October 1, 2018, and (4) Asia-Pacific. The time frame was restricted because clinical care and management options change with time.

Selection Criteria

In line with the primary outcome of the review, the main selection criteria included the burden of COPD reported in monetary terms or in terms of service use. No selection limits regarding the study design were adopted: both retrospective and prospective studies were considered acceptable. In terms of approaches, prevalence-based and incidence-based designs were retrieved and studies that used patient, society, or healthcare provider cost perspectives were included. In line with the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines, comorbidities of COPD were included.

Randomized controlled trials were excluded as they primarily focus on the assessment of efficacy and safety of a treatment rather than the overall population burden in the community. Studies evaluating the impact of pharmacological or non-pharmacological interventions on improvement or deterioration of health-related quality of life were excluded.

For studies that were identified as meeting the eligibility criteria, relevant data with cost methodologies, designs, and approaches were then extracted from each study by 2 reviewers independently and recorded on a predefined extraction grid, which was subsequently validated by an independent reviewer. Thereafter, all studies meeting the eligibility criteria were critically appraised using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[12]

Data Review and Analysis

The studies were reviewed in a 3-step process. First, the title list was identified and considered; then abstracts of those that passed the title review were screened and examined; and, finally, potentially relevant studies were reviewed for eligibility. The validity of the abstract selection was then confirmed by an independent reviewer outside the study team.

For MEDLINE and EMBASE studies, the following information was extracted: study design; type of costs ("direct–total"; "direct–inpatient"; "direct–ER visits"; "direct–treatment"; "direct–medications"; "direct–influenza vaccinations"; "indirect"); cost perspective (society, individual, healthcare provider);

Fig. 2 – Annual societal costs per capita of chronic obstructive pulmonary disease in Thailand, China, Taiwan, Singapore, Japan, and South Korea (in 2017 US$).

cost method ("cost of illness" and "weighted attribution"); cost approach ("prevalence-based" and "incidence-based"); and main findings. To facilitate comparison across studies carried out at different times and in different regions, all costs were adjusted for inflation and converted to 2017 US dollars using the national consumer price indexes.[13]

Quality Assessment

The quality of the included studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[12] For each study, the 24 reporting quality criteria were rated with a score of 1 if "yes" or 0 if "no."

Results

Search Strategy

Figure 1 summarizes the flowchart of the studies selection process for the systematic review in line with the PRISMA guidelines,[11] and Table 1 summarizes the cost studies of this review with 6 variables (study design, type of costs, cost perspective, cost method, cost approach, main findings). After removal of duplicates, 89 studies were screened for inclusion. Based on screening, 37 studies were eliminated. Among these, 20 studies were unrelated to COPD, 7 were unrelated to economic burden or costs, and 10 were unrelated to Asia-Pacific. The full text of the remaining 52 studies was evaluated. After a full text review, 42 studies were

rejected, leaving 10 studies on costs in Asia-Pacific to be in the final analysis.

These 10 studies[9,10,14–21] covered 6 countries with 11 estimates. Of the 10 studies, 8 studies[9,10,14–16,19–21] covered total societal costs (Japan, China, Taiwan, Thailand, Singapore, and South Korea), whereas 2 studies covered partial costs (Singapore and Taiwan). All 10 studies adopted the prevalence-based approach, 9 studies used the cost of illness (COI) approach in cost estimations, and 1 study[17] used the weighted-attribution method. Cross-country comparisons show wide variations in total societal cost estimates in Japan and South Korea (Fig. 2).

Quality Assessment

When the quality of each study was evaluated using the CHEERS checklist, all 10 selected studies were of good quality, with a mean score of 20 out of 24 (Table 2).

Only 1 study[16] of the 10 studies was retrospective and used discount rate or the present value, the current worth of a future sum of money or stream of cash flow given a specified rate of return (item 9); the rest were prospective studies. Nine studies failed to measure cost-effectiveness and did not include detailed methods used for identification of reference and synthesis of cost-effectiveness data. Only 1 study[14] did not fulfill item 17 (analytic methods) because the model-based economic evaluations failed to report how they transformed transition probabilities between events or health states into functions of age or disease severity. Three studies[14,17,18] failed to meet criteria 23 and 24 because they did not declare sources of funding or conflicts of interest.

Table 2 – Assessment of quality of studies.

Item	First author	Foo et al (2016)[15]	Kim et al (2016)[16]	Yoo et al (2016)[20]	Nishimura and Zaher (2004)[14]	Teo et al (2012)[17]	Wang et al (2016)[10]	Lin et al (2016)[19]	Chiang (2008)[18]	Fang et al (2018)[9]	Thanavirantananich et al (2016)[21]
1	Title	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2	Abstract	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3	Background and objectives	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
4	Target population and subgroups	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
5	Setting and location	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
6	Study perspective	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
7	Comparators	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
8	Time horizon	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
9	Discount rate	X	✓	X	X	X	X	X	X	X	X
10	Choice of health outcome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
11	Measurement of effectiveness	✓	X	X	X	X	X	X	X	X	X
12	Measurement and valuation of preference-based outcomes	✓	✓	✓	✓	✓	✓	✓	✓	X	✓
13	Estimating resources and costs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
14	Currency, price date, and conversion	✓	✓	✓	✓	✓	✓	✓	✓	✓	
15	Choice of model	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
16	Assumptions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
17	Analytic methods	✓	✓	✓	X	✓	✓	✓	✓	✓	✓
18	Study parameters	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
19	Incremental costs and outcomes	✓	X	X	✓	✓	X	X	✓	X	X
20	Characterizing uncertainly	✓	✓	X	✓	✓	X	X	✓	✓	X
21	Characterizing heterogeneity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
22	Study findings, limitations, generalizability, and current knowledge	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
23	Source of funding	✓	✓	✓	X	X	✓	✓	X	✓	✓
24	Conflicts of interest	✓	✓	✓	X	X	✓	✓	X	✓	✓
	Total score (maximum = 24)	23	22	20	19	20	20	20	20	20	20

Note. "✓" meets the quality assessment criteria; "X" does not fully conform to the quality assessment criteria.
CHEERS indicates Consolidated Health Economic Evaluation Reporting Standards.

Qualitative Critique: Micro-Economic Study

Japan: Nishimura and Zaher[14]

This study constructed a deterministic model using publicly available data to estimate the total societal costs of COPD for Japan. Model variables included direct medical utilization rates and costs, lost productivity, and severity. Strengths included (1) a comprehensive societal perspective and (2) a reasonable comprehensive time coverage of 12 years of literature search. Limitations included (1) using patient self-reported data that may be subjective; (2) lack of confirmatory data from multiple sources;

(3) exclusion of mild cases (moderate and severe participants were assumed to be primary users of inpatient and outpatient services and home oxygen therapy, but in practice some mild cases may also seek care); (4) ignoring multiple, recurrent hospitalizations (each patient was assumed to be hospitalized only once a year); (5) neglected the loss of work and income of caregivers; (6) ignored comorbidities; and (7) ignored indirect costs such as premature mortality. This study failed 5 quality assessment criteria items (Table 2). These included items 9 (discount rate) because it was a prospective study; 11 (measurement of effectiveness) because it did not include fully the methods for the identification of

Country	Japan (Nishimura and Zaher[14])	Japan (Foo et al[15])	South Korea (Kim et al[16])	South Korea (Foo et al[16])	South Korea (Yoo et al[20])
Table 3 – Summary of the direct and indirect costs of the 10 studies.					
Annual societal costs per capita ($2017)	4397.60	23 049	452.80	12 166.6	11 546.20
Severity					
Mild	X	✓	X	✓	✓
Moderate	✓	✓	✓	✓	✓
Severe	✓	✓	✓	✓	✓
Direct costs ($2017)	3518.10	10 833	265.30	973.30	2655.60
Inpatient/outpatient	✓	✓	✓	✓	✓
Emergency	✓	✓	X	✓	✓
Home oxygen therapy	✓	✓	X	✓	X
Medication	✓	✓	✓	✓	✓
Comorbidity	X	✓	X	✓	✓
Indirect costs ($2017)	879.5	12 216	187.5	11 193.30	8890.50
Loss in income (patient)	✓	✓	✓	✓	✓
Loss in income (caregiver)	X	X	X	X	X
Loss in income (early death)	X	✓	✓	✓	X

synthesis of cost-effectiveness data; and 17 (analytic methods) because it excluded methods for dealing with skewed and missing data. Items 23 and 24 (source of funding and conflicts of interest respectively) were not declared.

Singapore: Teo et al[17]

Teo and colleagues estimated direct costs in 2 public health clusters in Singapore for participants at least 40 years old (2005-2009). Model cost variables included inpatient, emergency department, specialist outpatient, and primary care. Strengths included (1) accounting for costs owing to comorbidities; (2) accounting for costs attributable to episodes of hospitalization for a primary diagnosis of COPD; (3) adopting the weighted-attribution costing approach instead of COI study for cost estimations of comorbidities; and (4) using the GOLD standard Chronic Disease Management Data-mart, based on the International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes (the Chronic Disease Management Data-mart is an enterprise-wide registry that harmonizes clinical health records across Tan Tock Seng Hospital, the National University Health Systems [NUHS], and the 9 National Healthcare Group [NHG] primary care clinics for specific chronic diseases); and (5) comprehensive coverage of administrative direct costs provided by data bases of disease management program and The Airway Program. The major limitation in this study was the underestimation of costs. The data-mart used in this study captured only costs in the NHG and NUHS and did not capture healthcare utilization costs in other health organizations if participants sought care elsewhere. This study failed 4 quality assessment criteria items: items 9 (discount rate); 11 (measurement of effectiveness) because it did not provide information on the time horizon over which participants were followed up and assessed; and 23 and 24 (declaration of source of funding and conflict of interests).

Japan and South Korea: Foo et al[15]

A cross-sectional population-based survey of participants at least 40 years old with comprehensive model cost variables (inpatient and outpatient hospitalizations, emergency visits, home oxygen therapy, medications, and lost work productivity) was adopted in this study. Strengths included the following: (1) societal study perspective, which was the most comprehensive of the studies reviewed; (2) using comprehensive methods of cost estimation for

indirect costs (the human capital and friction cost approaches); (3) using sensitivity analysis of total societal costs whereby the purchasing power parity, not market exchange rates, was used to convert national currencies into a standard currency (US$), avoided the volatility of the market-driven exchange rates, and tended to be more stable over time; (4) estimating the cost owing to comorbidity; (5) estimating mild, moderate, and severe participants; (6) using validated tests to measure estimated costs (mMRC grade—breathlessness; CAT score—health status); and (7) structured method (Work Productivity and Activity Impairment Questionnaire [WPAI]) to capture work loss by participants owing to COPD. Limitations included the following: (1) short study period of 1 year; (2) no explanation on the methodology of deriving the fixed cost assigned to each type of resource use because the accuracy of these cost estimates were crucial to the resultant total societal costs; (3) failure to capture every single resource use of parameter (eg, pulmonary rehabilitation, lung volume reduction surgery); (4) failure to monetize parameters recorded (eg, cost of all medications or all healthcare professional visits); (5) excluding out-of-pocket expenses such as nonprescription medication because these can be substantial if the government subsidized standard medication; (6) excluding indirect costs due to employed caregiver work loss; and (7) assumption of 100% work loss for participants after the effective retirement age because some of these participants may take up casual or part-time jobs.

South Korea: Kim et al[16]

Kim and colleagues adopted a retrospective study design. Formulas were used in total societal cost estimations with data from government and public institutions. Model variables included inpatient and outpatient hospitalizations, medications, and productivity loss. Strengths included the following: (1) a long 10-year study period; (2) using national-level health survey results, a macroeconomic statistics database, and health insurance claims database that cover the entire South Korean population; (3) societal perspective of study; (4) using national health insurance payouts, which will reflect more accurate estimates of direct medical costs; (5) indirect costs comprising loss of income owing to illness and early mortality of participants because most studies included only the former; and (6) wide age range with participants less than 40 years old up to at least 80 years old. Limitations included (1) estimated values of out-of-pocket expenses from

Table 3 – *continued*					
Singapore (Wang et al[10])	Singapore (Teo et al[17])	Taiwan (Chiang[18])	Taiwan (Lin et al[19])	China (Fang et al[9])	Thailand (Thanaviratananich et al[21])
2700.00	NA	NA	4000.0	3942.00	1105.30
✓	NA	X	✓	✓	✓
✓	NA	✓	✓	✓	✓
✓	NA	✓	✓	✓	✓
1080	2280	2372	1160	3469	829
✓	✓	✓	✓	✓	✓
✓	✓	✓	✓	✓	✓
X	X	✓	X	NA	X
✓	✓	✓	✓	✓	✓
✓	✓	X	✓	✓	✓
1620	NA	NA	2840	473	276.30
✓	NA	NA	✓	✓	✓
X	NA	NA	X	X	X
X	NA	NA	X	X	X

model and not actual expenses as the accuracy of these estimates depend heavily on the inputted values in the model; (2) ignoring undiagnosed, untreated mild cases; (3) ignoring caregivers' loss of time and income; and (4) ignoring emergency, home oxygen therapy, and comorbidities costs. This study failed 2 quality criteria items: 11 (measurement of effectiveness) and did not describe fully the methods used for the synthesis of cost-effectiveness data, and 19 (incremental costs and outcomes) because it failed to report mean values for the main categories of estimated costs and outcomes of interests. Outcomes were discounted at an annual rate of 5%, which was similar to a wage increase rate of 4.8% to 5.4% for the past 4 to 5 years in South Korea.

China: Fang et al[9]
To date, this is the only study that covered total societal costs on 7 major regions in China, whereas many studies covered individual provinces on total societal costs.[22–24] Direct variables covered mild, moderate, and severe conditions with comorbidities using inpatient and outpatient services, emergency, and medication. Indirect costs included loss in income of patients. Strengths included the following: (1) large sample size of 66 752 participants, which was a nationally representative sample of the general population of China, and (2) using spirometry with both pre-bronchodilator and postbronchodilator assessments for the diagnosis of COPD, which was more objective than self-reported results. Limitations included the following: (1) excluding non-permanent residents because of sampling design; (2) excluding participants with extreme severe conditions (for safety) for spirometry and postbronchodilator test; (3) smoking status was self-reported and not validated; and (4) misclassification of people with asthma and other disease as having COPD. This study failed the following 4 quality criteria items: items 9 (discount rate); 11 (measurement of effectiveness) because it failed to provide methods of data collection of study participants in 7 provinces of China with different cultures, socioeconomic, and genetic conditions; 12 (measurement and valuation of preference-based outcomes) because authors failed to describe the population from which valuations were obtained in terms of size and demographics characteristic; and 19 (incremental costs and outcomes) as it failed to report the mean values of the estimated costs and outcomes of interest.

Taiwan: Chiang[18]
Chiang adopted a prospective direct cost study over a 1-year period for moderate and severe participants in Taiwan (2002 to 2003). Direct costs included inpatient and outpatient services, emergency, home oxygen therapy, and medication. Strengths included the following (1) using GOLD standard to assess the severity of COPD, and (2) using COI analysis for estimation of direct costs. Limitations included the following: (1) participants from a single tertiary healthcare center and may not be a representative of the general population of people with COPD; (2) excluding mild participants; (3) excluding comorbidities, and (4) small sample size of 160 study participants. This study failed 4 quality criteria items: 9 (discount rate); 11 (measurement of effectiveness) because it failed to provide methods of data collection of study participants; and 23 and 24 because authors failed to declare the source of funding and conflicts of interest, respectively.

Thailand: Thanaviratananich et al[21]; Singapore: Wang et al[10]; Taiwan: Lin et al[19]; and South Korea: Yoo et al[20]
These 4 studies were part of an Asia-Pacific Burden of Respiratory Disease (APBORD) study covering 6 countries. The Asia-Pacific Burden of Respiratory Disease study was a cross-sectional, observational study that examined the disease and economic burden of allergic rhinitis, asthma, COPD, and rhinosinusitis across Asia-Pacific using 1 standard protocol. All studies used a prospective cross-sectional analysis of direct and indirect costs of participants with mild, moderate, and severe COPD during a 1-year period (2012-2013). Direct costs included inpatient and outpatient services, emergency, medication, and comorbidities, and indirect costs included loss of income of participants. Strengths included the following: (1) societal perspective; (2) comprehensive structured methods to capture indirect costs (WPAI-SHP) owing to productivity loss as a result of absenteeism (work-time lost) and presenteeism (lost on-the-job productivity); and (3) large sample size of 5250 participants in Singapore.[10] Limitations included the following: (1) participants were from primary health physicians and specialists in urban areas and may not be representative of the rural population in Thailand,[21] and (2) small sample sizes of 1000 participants in Thailand, 1001 in Taiwan,[19] and 999 in South Korea.[20] These studies failed 4 assessment criteria: 9 (discount rate); 11 (measurement of

effectiveness) because it failed to provide methods of data collection of study participants of different disease severity; 19 (incremental costs and outcomes) because authors failed to provide means of the estimated costs of mild, moderate, and severe COPD; and 20 (characterizing uncertainly) because the authors failed to provide sensitivity analysis to capture uncertainty related to sampling variability.

Cross-country cost comparisons

Table 3 summarizes the direct and indirect costs of the 10 studies. The principal finding was that the annual cost estimates of COPD per capita in 2017 for Asia-Pacific were high ($2700 in Singapore, $3942 in China, $4000 in Taiwan, $12 166 in South Korea, $23 049 in Japan) compared with non–Asia-Pacific countries ($2490 in Canada, $3487 in USA, and $11 850 in UK).[25] In particular, cross-country cost estimates were higher for 2 Asia-Pacific countries (Japan and South Korea) compared with UK.

Cross-country cost comparisons

Variations in cross-country cost estimations were attributable to inconsistency in estimations by disease severity, variations in cost components, data limitation, and methodologies.

Disease Severity

Two different sets of estimates resulted for Japan. Nishimura and Zaher[14] estimated the average annual total cost per capita for moderate and severe COPD to be $4397.60 (80% direct and 20% indirect costs) compared with Foo et al,[15] $23 049 per capita (47% direct and 53% indirect costs) for mild, moderate, and severe COPD (Fig. 2). The stages of disease severity contributed to differences in cost estimates.

Variation in Cost Components

There were 3 sets of cost estimates for South Korea. Annual societal cost per capita ranged widely from $452.80 to $12 167. Foo et al's[15] estimated cost was $12 167 (92% indirect and 8% direct), and Kim et al's[16] was at the lowest range of $452.80 (41.4% indirect and 58.6% direct). Yoo et al's[20] estimate ($11 546) was very similar to Foo et al's, except that the former excluded premature mortality and home oxygen therapy. Cost estimations in Foo et al[15] were the most comprehensive of the 3 studies because this study included the majority of the direct and indirect cost components (Table 3).

Variation in Methods

It is difficult to compare methods because authors were not explicit in identifying them. Foo et al's[15] estimate of indirect cost was the highest in South Korea by using both the human capital and friction cost approaches, whereas Kim et al's[16] estimate was the lowest by using formulas, and not actual expenses, as inputs with the discount rate to calculate loss of future income owing to premature death.

Studies used different International Classification of Disease (ICD) versions and disease codes, but there were no major changes and a group of them[9,14,15,18] did not include the ICD codes.

Discussion

This review found that participants with mild and severe COPD placed a high economic burden on the healthcare system in the majority of these countries (with the exception of Thailand) compared with non–Asia-Pacific countries. In particular, cross-country cost comparison in terms of annual societal costs per capita was greatest for 2 countries (Japan and South Korea) compared with non–Asia-Pacific countries. These 2 non–Asia-

Pacific countries (UK and USA) were selected for comparison in this systematic review after Landis et al's study,[7] where non–Asia-Pacific countries (UK and USA) were compared with Asia-Pacific countries (Japan and South Korea) in terms of estimated COPD prevalence. Participants in these Asia-Pacific countries tended to have higher indirect costs, mainly driven by higher national per-capita incomes. Other factors influencing variations in cost data could be those related to cultural and healthcare practices. Participants in Japan and South Korea reported the lowest levels of symptoms, but both had the highest proportion of participants treated under specialist care (28%) and inpatient hospitalization (26%), respectively.[15] Two countries in this study (Japan and China) included participants with mild disease and yet had the highest direct costs. Direct costs in these 2 countries were likely to be driven by healthcare systems and participants' access to healthcare. Fang and colleagues[9] covered costs in 7 major regions in China and these direct cost estimate results will likely be different if the study has a wider coverage including participants in regions of Southeast and Western China. Economic burden is also poorly quantified and reported in the Asia-Pacific. The high-quality assessment mean score of these 10 studies coupled with the many limitations in each qualitative critique may indicate that these studies methodologically appeared strong but their utilities are limited. In some studies,[26–30] variations in cost estimates were attributable to higher smoking rates but smoking rates were not reported in the studies reviewed. Mortality rates of COPD owing to smoking in China (30.21%), Taiwan (25.68%), and Thailand (22.09%) were higher than the global mortality rate of COPD (16.95%) in 2016.[31] Wide variations in cost estimates exist owing to variation in smoking rates, cost components, methods, limitations of data, and different disease severity. We propose that researchers conducting burden-of-Illness studies use standardized methods and reporting formats to support cross-country comparisons.

This review highlights 3 shortcomings in the literature. First, there was a lack of consistency in the classification of subject and disease groupings in ICD, making it difficult to analyze cross-country comparisons. Second, it is important to consider indirect costs when assessing the burden or costs of COPD. Indirect costs are "hidden" burdens of COPD often ignored by decision makers while making policy decisions. Third, the lack of a proper administrative database in Asia-Pacific to provide services of administrative claims for direct cost estimation may result in cost estimation bias.

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