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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. The aim of this paper is to assess cost studies of COPD and analyse 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 \$4,398 – \$23,049 per capita in Japan and \$453 – \$12,167 in South Korea. For the remaining countries, there was only one estimate (Singapore: \$2,700; Taiwan: \$4,000; China: \$3,942; and Thailand: \$1,105). In addition, there were estimates of partial costs in Singapore & Taiwan.

Conclusions Results of this review showed high cost variations between countries, with estimates in two countries (Japan, 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 in order to support cross-country comparisons.

Keywords

Asia-Pacific, Chronic obstructive pulmonary disease, direct costs, indirect costs, societal costs

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 which 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 health care utilization [4-5]. COPD imparts a significant disease burden in Asia-Pacific. This literature review covered six countries in Asia-Pacific (South Korea, Japan, China, Taiwan, Singapore, and Thailand). The prevalence rate of COPD in Asia-Pacific was 6.2% [6], almost on par with 6.7% in USA [7]. Across the region, prevalence rates (Table 1) ranged from a low of 5.3% in Thailand [6], 5.9% in Singapore [6], 6.1% in Taiwan [9], 7% in Japan, 8.2% in South Korea [7] to a high of 13.6% in China [8]. 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%). However, there was less variation in societal costs of respiratory diseases amongst countries [10] (39-71% of average wages). This might be due to lost work productivity rather than direct health care costs being the biggest contributor to overall costs for illnesses. Low direct costs in countries like Singapore (where government subsidises partial medication costs in public clinics) may be offset by high indirect costs (labour costs or paid helpers), while countries like Thailand may have high direct costs (medication costs) but relatively low indirect costs (e.g., informal care by family members).

The aim of this paper 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 carried out through a comprehensive search of databases in Excerpta Medica Database (EMBASE) and PubMed Medical Literature Analysis and Retrieval System Online (MEDLINE) from 1 October 2000 to 1 October 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.

Search Strategy

For both MEDLINE and EMBASE database library studies, the following MeSH and Emtree terms “Bronchitis, Chronic/ or pulmonary disease”, “Asia-pacific” and “Direct Service Costs/ or cost of illness/ or health care costs/ or health expenditures” were combined with key words “chronic bronchitis or COPD,” and “systematic review or methodology or economic burden.” The search criteria were (i) English language, (ii) Human subjects, (iii) 1 October 2000 to 1 October

2018 and (iv) Asia-Pacific. The time frame was restricted as 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 and/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 (RCTs) 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/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 two reviewers independently and recorded on a pre-defined 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 three-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' and 'indirect'); cost perspective (society, individual, healthcare provider); cost method ('cost of illness' and 'weighted attribution'); cost approach ('prevalence-based' and 'incidence-based'); and main findings. In order 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 zero if 'no' .

RESULTS

Search Strategy

Fig. 1 summarized the flow chart of the studies selection process for the systematic review in line with the PRISMA guidelines [11], while Table 2 summarized the cost studies of this review with six 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 not related to COPD, 7 not on economic burden or costs and 10 not on 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 [8, 10, 14-21] covered 6 countries with 11 estimates. Out of the 10 studies, 8 studies [8, 10, 14-16, 19-21] covered total societal costs (Japan, China, Taiwan, Thailand, Singapore, and South Korea) while 2 studies covered partial costs (Singapore & Taiwan). All 10 studies adopted the prevalence-based approach, 9 studies used the cost of illness (COI) approach in cost estimations and one study [17] used the weighted attribution method. Cross country comparisons show wide variations in total societal cost estimates in Japan and South Korea (Figure 2).

Quality Assessment

When the quality of each study was evaluated using the CHEERS checklist, all ten selected studies were of good quality, with a mean score of 20/24 (Table 3).

Only one [16] of the ten studies was retrospective and used discount rate (item 9) :the rest were prospective studies. Nine studies failed to measure effectiveness and did not include detailed methods used for identification of reference and synthesis of clinical effectiveness data. Only one [14] did not fulfil item 17 (analytic methods) as 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 & 24 as they did not declare sources of funding or conflicts of interest.

Qualitative Critique: Micro-economic study

Critique of each study was conducted, focussing on strengths, weaknesses, and quality of assessment.

Japan: Nishimura & Zaher (2004) [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 i) a comprehensive societal perspective and ii) a reasonable comprehensive time coverage of 12 years of literature search. Limitations included i) using patient self-reported data which may be subjective; ii) lack of confirmatory data from multiple sources; iii) exclusion of mild cases (moderate and severe patients were assumed to be primary users of inpatient & outpatient services and home oxygen therapy but in practice some mild cases may also seek care); iv) ignoring multiple, recurrent hospitalizations. Each patient was assumed to be hospitalized only once a year; v) neglected the loss of work and income of caregivers; vi) ignored comorbidities and vii) ignored indirect costs like premature mortality. This study failed five quality assessment criteria items (Table 3). These included items 9 (discount rate) as it was a prospective study; 11 (measurement of effectiveness) as it did not include fully the methods for the identification of synthesis of clinical data; 17 (analytic methods) as it excluded methods for dealing with skewed, and missing data, and items 23 & 24 (source of funding and conflicts of interest respectively) were not declared.

Singapore: Teo et al., (2012)[17]

Teo and colleagues estimated direct costs in two public health clusters in Singapore for patients at least 40 years old (2005 to 2009). Model cost variables included inpatient, emergency department,

specialist outpatient, and primary care. Strengths included i) accounting for costs due to co-morbidities; ii) accounting for costs attributable to episodes of hospitalization for a primary diagnosis of COPD; iii) adopting the weighted attribution costing approach instead of COI study for cost estimations of comorbidities; iv) using the GOLD standard Chronic Disease Management Data-mart (CDMD), based on the International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes. The CDMD is an enterprise-wide registry that harmonizes clinical health records across Tan Tock Seng Hospital, the National University Health Systems (NUHS) and the nine National Healthcare Group (NHG) primary care clinics for specific chronic diseases and v) comprehensive coverage of administrative direct costs provided by data bases of Disease Management (DM) programme and The Airway Program (TAP). The major limitation in this study was the underestimation of costs. The data-mart used in this study only captured costs in the NHG and NUHS and does not capture health care utilization costs in other health organizations if patients sought care elsewhere. This study failed four quality assessment criteria items; including items 9 (discount rate); 11 (measurement of effectiveness) as it did not provide information on the time horizon over which patients were followed up and assessed; 23 and 24 (declaration of source of funding and conflict of interests).

Japan & South Korea: Foo et al., (2016)[15]

A cross-sectional population based survey of patients at least 40 years old with comprehensive model cost variables (inpatient and outpatient hospitalisations, emergency visits, home oxygen therapy, medications and lost work productivity) was adopted in this study. Strengths included i) societal study perspective which was the most comprehensive of the studies reviewed; ii) using comprehensive methods of cost estimation for indirect costs (the human capital and friction cost approaches); iii) using sensitivity analysis of total societal costs whereby the purchasing power

parity instead of market exchange rates was used to convert national currencies into a standard currency (US\$); and avoided the volatility of the market-driven exchange rates and tended to be more stable over time; iv) estimating the cost due to comorbidity; v) estimating mild, moderate and severe patients; vi) using validated tests to measure estimated costs (mMRC grade–breathlessness;CAT score-health status) and vii) structured method (Work Productivity and Activity Impairment Questionnaire-WPAI) to capture work loss by patients due to COPD. Limitations included i) short study period of 1-year; ii) no explanation on the methodology of deriving the fixed cost assigned to each type of resource use as the accuracy of these cost estimates were crucial to the resultant total societal costs; iii) failure to capture every single resource use of parameter (e.g. pulmonary rehabilitation, lung volume reduction surgery); iv) failure to monetise parameters recorded (e.g. cost of all medications or all healthcare professional visits); v) excluding out-of-pocket expenses such as non-prescription medication as these can be substantial if government subsidised standard medication; vi) excluding indirect costs due to employed caregiver work loss; vii) assumption of 100% work loss for patients after the effective retirement age as some of these patients may take up casual or part-time jobs.

South Korea: Kim et al., (2016) [16]

Kim and colleagues adopted a retrospective study design. Formulae 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 i) a long 10-year study period; ii) using national-level health survey results, a macroeconomic statistics database and health insurance claims database which cover the entire South Korean population; iii) societal perspective of study; iv) using national health insurance payouts which will reflect more accurate estimates of direct medical costs; v) indirect costs comprising loss of

income due to illness and early mortality of patients, as most studies included only the former; and vi) wide age range with patients less than 40 years old up to at least 80 years old. Limitations included i) estimated values of out-of-pocket expenses from model and not actual expenses as the accuracy of these estimates depend heavily on the inputted values in the model; ii) ignoring undiagnosed, untreated mild cases; and iii) ignoring caregivers' loss of time and income; iv) ignoring emergency, home oxygen therapy and comorbidities costs. This study failed two quality criteria items 11 (measurement of effectiveness) and did not describe fully the methods used for the synthesis of clinical effectiveness data; and 19 (incremental costs and outcomes) as it failed to report mean values for the main categories of estimated costs and outcomes of interests. Outcomes were discounted at an annul rate of 5%, which was similar to a wage increase rate of 4.8 – 5.4% for the past 4-5 years in South Korea.

China: Fang et al., (2018) [8]

To-date, this is the only study which covered total societal costs on the most number of 7 major regions in China, while many studies covered individual provinces on total societal costs [22-24] Direct variables covered mild, moderate and severe conditions with comorbidities utilising inpatient/outpatient services, emergency, and medication. Indirect costs included loss in income of patient. Strengths included i) large sample size of 66,752 patients which was a nationally representative sample of the general population of China, and ii) using spirometry with both pre-bronchodilator and post-bronchodilator assessments for the diagnosis of COPD, which was more objective than self-reported results. Limitations included i) excluding non-permanent residents because of sampling design; ii) excluding patients with extreme severe conditions (for safety) for spirometry and post-bronchodilator test; iii) smoking status was self-reported and not validated and iv) misclassification of people with asthma and other disease as having COPD. This study

failed four quality criteria items. These included items 9 (discount rate); 11 (measurement of effectiveness) as it failed to provide methods of allocation of study subjects in 7 provinces of China with different cultures, socioeconomic and genetic conditions of subjects; 12 (measurement and valuation of preference-based outcomes) as 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 failed to report the mean values of the estimated costs and outcomes of interest.

Taiwan: Chiang (2008) [18]

Chiang adopted a prospective direct cost study over a 1-year period for moderate and severe patients in Taiwan (2002 to 2003). Direct costs included inpatient/outpatient services, emergency, home oxygen therapy and medication. Strengths included i) using GOLD standard to assess the severity of COPD; and ii) using COI analysis for estimation of direct costs. Limitations included i) patients were from a single tertiary health-care centre and may not be a representative of the general population of people with COPD; ii) excluding mild patients; iii) excluding co-morbidities, and iv) small sample size of 160 study subjects. This study failed four quality criteria items. These included items 9 (discount rate); 11 (measurement of effectiveness) as it failed to provide methods of allocation of study subjects; and 23 and 24 as authors failed to declare the source of funding and conflicts of interest, respectively.

Thailand: Thanaviratananich et al., (2016) [21], Singapore: Wang et al., (2016) [10], Taiwan: Lin et al., (2016) [19] and South Korea: Yoo et al., (2016) [20]

These 4 studies were part of a Asia-Pacific Burden of Respiratory Disease (APBORD) covering 6 countries. All studies used a prospective cross-sectional analysis of direct and indirect costs of patients with mild, moderate and severe COPD during a 1-year period (2012-2013). Direct costs

included inpatient/outpatient services, emergency, medication and co-morbidities and indirect costs included loss of income of patients. Strengths included i) societal perspective; ii) comprehensive structured methods to capture indirect costs (WPAI-SHP) due to productivity loss as a result of absenteeism (work-time lost) and presenteeism (lost on-the-job productivity); and iii) large sample size of 5,250 patients in Singapore [10]. Limitations included i) patients were from primary health physicians and specialists in urban areas and may not be representative of the rural population in Thailand [21]; ii) small sample sizes of 1,000 patients in Thailand, 1,001 in Taiwan [19] and 999 in South Korea [20]; and iii) loss of income from premature mortality. These studies failed 4 assessment criteria. These included items 9 (discount rate); 11 (measurement of effectiveness) as it failed to provide methods of allocation of study subjects of different disease severity; 19 (incremental costs and outcomes) as authors failed to provide means of the estimated costs of mild, moderate and severe COPD; and 20 (characterising uncertainty) as the authors failed to provide sensitivity analysis to capture uncertainty related to sampling variability.

Table 4 summarized the direct and indirect costs of the 10 studies. The principal finding was the annual cost estimates of COPD per capita in 2017 for Asia-Pacific were high (\$2,700 in Singapore, \$3,942 in China, \$4,000 in Taiwan, \$12,166 in South Korea, \$23,049 in Japan) compared to non-Asia-Pacific countries (\$2,490 in Canada, \$3,487 in USA and \$11,850 in the UK) [31], (Table 5). In particular, cross country cost estimates were higher for two Asia-Pacific countries (Japan and South Korea) compared to UK. Variations in cross country cost estimations were attributable to inconsistency in estimations by disease severity, variations in cost components, data limitation and methodologies.

Cross country cost comparisons

Disease Severity

Two different sets of estimates resulted for Japan. Nishimura & Zaher (2004) [14] estimated the average annual total cost per capita for moderate/severe COPD to be \$4,397.6 (80% direct and 20% indirect costs) compared with Foo et al., [15] \$23,049 per capita (53% indirect and 47% direct costs) for mild/moderate/severe COPD (Fig. 2). The stages of disease severity contributed to differences in cost estimates.

Variation in cost components

Three sets of cost estimates resulted for South Korea. Annual societal cost per capita ranged widely from \$452.8 to \$12,167. Foo et al., (2016) [15] estimated cost was \$12,167 (92% indirect and 8% direct) while Kim et al., (2016) [16] was at the lowest range of \$452.80 (41.4% indirect and 58.6% direct). Yoo et al., [20] estimate (\$11,546) was very similar to Foo's except the former excluded premature mortality and home oxygen therapy. Cost estimations in Foo et al., (2016) [15] were the most comprehensive of the three studies as this study included majority of the direct and indirect cost components (Table 4).

Variation in Methods

It is difficult to compare methods because authors were not explicit in identifying them. Foo et al., (2016) [15] used both the human capital and friction cost approaches in estimating indirect costs in South Korea due to absenteeism while Yoo's study included absenteeism and presenteeism. Kim et al., (2016) [16] used formulae in cost estimations and not actual expenses; and discount rate to calculate loss of future income due to premature death.

International Statistical Classification of Disease and Related Health Problem (ICD)

Studies used different ICD versions and disease codes but there were no major changes and a group of them [8, 14, 15, 18] did not include the ICD codes.

DISCUSSION

This review found that COPD placed a high economic burden on the healthcare system in majority of these countries (with the exception of Thailand) compared to non-Asia-Pacific countries. In particular, cross country cost comparison in terms of annual societal costs per capita was greatest for two countries (Japan and South Korea) compared to non- Asia-Pacific countries. Patients in these countries tended to have higher indirect costs, mainly driven by higher national per capita incomes. Other factor influencing variations in cost data could be those related to cultural and healthcare practices. Patients in Japan and South Korea reported the lowest levels of symptoms but both had the highest proportion of patients treated under specialist care (28%) and inpatient hospitalization (26%) respectively [15]. Two countries (Japan and China) in this study included patients with mild disease and yet had the highest direct costs. Direct costs in these two countries were likely to be driven by healthcare systems and patients' access to healthcare. Fang and colleagues 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 patients in regions of Southeast and Western China. Economic burden is also poorly quantified and reported in 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. Variations in cost estimates were attributable to higher smoking rates [25-29]. Mortality rates of COPD due 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 [30]. Wide variations in cost estimates exist due to variation in smoking rates, cost components, methods, limitation of data and different disease severity. We propose that researchers conducting Burden of Illness studies use standard methods and reporting formats in order to support cross-country comparisons.

This review highlights three shortcomings in the literature. Firstly, there was a lack of consistency in the classification of subject and disease groupings in ICD, making it difficult to analyse cross-country comparisons. Secondly, it is important to consider indirect costs when assessing the burden or costs of COPD. Indirect costs are “hidden” burden of COPD often ignored by decision makers whilst making policy decisions. Thirdly, the lack of a proper administrative data base in Asia-pacific to provide services of administrative claims for direct cost estimation may result in cost estimation bias.

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Table 1: Prevalence rates in Asia-Pacific (2012 – 2015)

Country	Prevalence rates (%)
Thailand [6]	5.3
Singapore [6]	5.9
Taiwan [9]	6.1
Japan [7]	7.0
South Korea [7]	8.2
China [8]	13.6
Asia-Pacific [6]	6.2

Figure 1. Flow diagram of the selection process of studies for the systematic review, in line with the PRISMA guidelines

Figure 2. Annual societal costs per capita of COPD in Thailand, China, Taiwan, Singapore, Japan and South Korea (in 2017 US\$)

Table 2. 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. 4,343 subjects aged 40 years and older with mild, moderate and severe COPD from 2012-2013. Direct costs were based those requiring emergency departments, outpatient & inpatient services, home oxygen therapy, medication and co morbidity. 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\$ 8,324.50 for South Korea (2013). Indirect costs contributed 53% and direct costs 47% in Japan, while in South Korea, indirect cost was 92% and direct cost was 8%.
Teo et al., 2012 [17]	Prospective - Analysis of hospitalization episodes and co-	Direct	Healthcare provider	Weighted attribution	Prevalence-based	The annual direct cost of 2 health care clusters in Singapore was US\$11 million

Singapore	morbidities from public databases. 5,125 subjects aged 40 years and over from 2005 to 2009. Direct costs were from utilization of health services in inpatient & outpatient, emergency department, and co morbidity.					(2009), with inpatients hospitalization contributing 68% and 32% from emergency, specialist outpatient and primary care visits. The annual direct cost per capita was US\$2,280.
Wang et al., 2016 [10] Singapore (APBORD study)	Prospective –Cross analysis of direct & indirect costs of 5,250 patients >= 18 years at 22 study sites for 1 year from 2012-2013. Direct costs included visits to inpatient/outpatient services, emergency, medication and co morbidity. Indirect costs included loss in income from patient (absenteeism) and loss of productivity while working (presenteeism)	Total	Societal	Cost of illness	Prevalence-based	The annual total societal cost per capita was \$4,500 (60% indirect and 40% direct costs).

Nishimura & Zaher, 2004 [14] Japan	Prospective – Analysis of direct and indirect costs by building a deterministic model using publicly available data from 1990-2002. Moderate to high severity of COPD patients 40 years and over. Direct costs consist of inpatient & 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 US\$ 3,694 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 – 2013. 10-year mean number of 1,264,140 subjects with no age limit with moderate and severe COPD. Direct costs consisted inpatient/outpatient services and	Total	Societal	Cost of illness	Prevalence-based	The annual societal cost of COPD was US\$439.9 million (2013), with 41.4% of indirect costs and 58.6% of direct costs. The annual societal cost per capita was US\$309.8.

	medication. Indirect costs consisted of productivity loss due to missed day's worked and premature mortality.					
Yoo et al., 2016 [20] South Korea (APBORD study)	Prospective – Cross sectional analysis of direct & indirect costs of 999 patients ≥ 18 years at 8 study sites for 1 year from 2012-2013. Same direct and indirect costs components as Wang et al. (2016) study.	Total	Societal	Cost of illness	Prevalence-based	The annual total societal cost per capita was \$7,900 (77% indirect and 23% direct costs).
Lin et al., 2016 [19] Taiwan (APBORD study)	Prospective – Cross sectional analysis of direct & indirect costs of 1,001 patients ≥ 18 years at 8 study sites for 1 year from 2012-2013. Same direct and indirect costs components as Wang et al.'s (2016) study.	Total	Societal	Cost of illness	Prevalence-based	The annual total societal cost per capita was \$8,000 (71% indirect and 29% direct costs).
Chiang, 2008 [18] Taiwan	Prospective - Analysis of hospitalization episodes from	Direct	Societal	Cost of illness	Prevalence-based	The mean total direct costs per capita were US\$1,092, US\$4,258 and

	medical records. 160 subjects aged 40 years and over for 1-year from 2002 to 2003. Direct costs were from annual utilization of health services in inpatient & outpatient, clinic visits and emergency department.					US\$8,252 for moderate A, moderate B and severe COPD patients respectively.
Fang et al., 2018 [8] 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 US\$1,964 – US\$3,449 per capita (2014-2015). Prevalence rate was 13.6% (using post-bronchodilator test).
Thanavirantananich et al, 2016 [21] Thailand (APBORD study)	Prospective – Analysis of direct & indirect costs of 1,995 patients >= 18 years at 4 study sites for 1 year from 2012-2013. Same direct and indirect costs components as Wang et al. (2016) study.	Total	Societal	Cost of illness	Prevalence based	Annual total societal cost of COPD was US\$3,000 per capita (2013), with US\$750 (25%) indirect and US\$2,250 (75%) direct costs.

Table 3: Assessment of Quality of Studies

Item	First Author	Foo et al., 2016 [15]	Kim et al., 2016 [16]	Yoo et al., 2016 [20]	Nishimura & 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[8]	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	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗
10	Choice of health outcome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
11	Measurement of effectiveness	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
12	Measurement and valuation of preference-based outcomes	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓
13	Estimating resources and costs	✓	✓	✓	✓	✓	✓	✓	✓		✓
14	Currency, price date and conversion	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
15	Choice of model	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
16	Assumptions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
17	Analytic methods	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓
18	Study parameters	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
19	Incremental costs and outcomes	✓	✗	✗	✓	✓	✗	✗	✓	✗	✗
20	Characterising uncertainty	✓	✓	✗	✓	✓	✗	✗	✓	✓	✗
21	Characterising heterogeneity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
22	Study findings, limitations, generalizability and current knowledge	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
23	Source of funding	✓	✓	✓	✗	✗	✓	✓	✗	✓	✓
24	Conflicts of interest	✓	✓	✓	✗	✗	✓	✓	✗	✓	✓
	Total Score (maximum =24)	23	22	20	19	20	20	20	20	20	20

Note: “✓” meets the quality assessment criteria, “✗” does not fully conform to the quality assessment criteria. CHEERS: Consolidated Health Economic Evaluation Reporting Standards

Table 4: Summary of the direct and indirect costs of the 10 studies

Country	Japan (Nishimura & 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]	Singapore (Wang et al.) [10]	Singapore (Teo et al.) [17]	Taiwan (Chiang) [18]	Taiwan (Lin et al.) [19]	China (Fang et al.) [8]	Thailand (Thanaviratananich et al.,) [21]
Annual societal costs per capita (US\$2017)	4,397.6	23,049	452.8	12,166.6	11,546.20	2,700.0	N.A	N.A	4,000.0	3,942.0	1,105.3
Severity											
• Mild	X	✓	X	✓	✓	✓	N.A	X	✓	✓	✓
• Moderate	✓	✓	✓	✓	✓	✓	N.A	✓	✓	✓	✓
• Severe	✓	✓	✓	✓	✓	✓	N.A	✓	✓	✓	✓
Direct costs (US\$2017)	3,518.1	10,833	265.3	973.3	2,655.6	1,080.0	2,280	2,372.0	1,160.0	3,469.0	829.0
• Inpatient/Outpatient	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Emergency	✓	✓	X	✓	✓	✓	✓	✓		✓	✓
• Home Oxygen Therapy	✓	✓	X	✓	X	X	X	✓	X	N.A	X
• Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Co-morbidity	X	✓	X	✓	✓	✓	✓	X	✓	✓	✓
Indirect costs (US\$2017)	879.5	12,216	187.5	11,193.3	8,890.5	1,620.0	N.A	N.A	2,840.0	473	276.3
• Loss in income (patient)	✓	✓	✓	✓	✓	✓	N.A	N.A	✓	✓	✓
• Loss in income (caregiver)	X	X	X	X	X	X	N.A	N.A	X	X	X
• Loss in income (early death)	X	✓	✓	✓	X	X	N.A	N.A	X	X	X

Table 5: Annual societal costs of COPD in Asia-pacific compared to non-Asia-pacific countries

Country	Annual societal costs per capita (2017 US\$)
Thailand	1,105
Singapore	2,700
China	3,942
Taiwan	4,000
South Korea	12,167
Japan	23,049
Canada [31]	2,490
USA [31]	3,487
UK [31]	11,850

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