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Cost of Illness Study in Thyroid Patients: A Systematic Review

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Abstract
Background*: The thyroid has a vital role in growth, neurodevelopment, reproduction, and metabolism. About 300 million people around the world had been reported to be suffering from thyroid disorders, but more than half were unaware. The factors of sex, age, weight of disease, and other accompanying conditions should be considered, otherwise, it will cause a long time treatment period in which the cost will become higher from year to year.* ***Purpose****: The systematic review aims to provide an overview of the financial burden caused by thyroid disease for the communities, governments and health care providers.* ***Method****: A systematic review of publications in several databases, namely PUBMED, SCIENCE DIRECT, DOAJ, SCOPUS and GOOGLE SCHOLAR. Results: Six research articles were obtained from publications selected for systematic review. The reviewed articles show overviews of the cost of thyroid disease in several countries. The financial burden of thyroid patients in some countries varies, with different perspectives. The lowest to highest cost ranges from 0.125 USD/patient – 8106 USD/patient. Conclusion: The study in this review illustrates the various costs in different countries; the cost of screening, and thyroid surgery has the largest contribution compared to other costs; research on the financial burden suffered by thyroid patients in the future must be carried out continuously and periodically to be able to estimate the cost of therapy more appropriately to provide a useful data for health care providers, governments and the community. Direct medical costs are the largest proportion.*

Keywords*: thyroid, cost of disease, cost analysis, the economic cost burden*

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INTRODUCTION

Thyroid gland disease is a public health problem worldwide. The imbalance in the hormone system can lead to many diseases, from raised bumps to life-threatening diseases, such as thyroid cancer (Awad *et al*., 2016). Iodine deficiency is the most common cause of thyroid disease. Iodine deficiency has several side effects on human growth and development, called *iodine deficiency disorders (IDDs)*, resulting from inadequate thyroid hormone production. The *iodine deficiency disorders (IDDs) mitigation* program started from the decade of 1990 through the *salt* iodization strategy or "berry salt for all" (Zimmermann & Andersson, 2021).

The manifestations of thyroid disorders vary greatly and depend on the type of thyroid hormone disorder. The manifestations of thyroid disorders differ, particularly hyperthyroidism and hypothyroidism. Factors affecting TSH and thyroid hormone include genetic factors, demographic factors such as age and gender, intrinsic factors (stress), drugs and environmental/*lifestyle factors* (*smoking*, alcohol consumption) (Leko et al., 2021). Symptoms in patients with hyperthyroidism disorders are anxiety, confusion, diarrhoea, palpitations, chest pain, hair loss, and diplopia, while in hypothyroidism, the symptoms are fast tiredness, slow mind, dry skin, constipation, increased weight, not resistant to cold (Indonesian Thyroid Association, 2022).

Hypothyroidism, hyperthyroidism (thyrotoxicosis), and nodular goitre are just a few hormonal manifestations and functions of different thyroid disorders (National Institute for Health and Care Excellence, 2019). Thyroid dysfunction, including hyperthyroidism and hypothyroidism, can affect the circulatory system by affecting cardiac output, contractility, blood pressure, vascular resistance, and rhythm disturbances, ultimately resulting in heart failure, fibrillation, and congestive heart failure (Awad *et al.*, 2016).

According to epidemiological studies, the prevalence of hyperthyroidism and hypothyroidism ranges from 0.1 to 1.25% and 0.25 to 4.20% worldwide (Taylor *et al.*, 2018). The prevalence of thyroid nodules rises with age and body mass index, and they are four times more common in women than in men. Approximately 90 to 95% of thyroid nodules are benign (Kant *et al.*, 2020).

Thyroid cancer incidence nearly tripled from 4.9 cases per 100,000 people in 1975 to 14.3 cases per 100,000 people in 2009. Since the middle of the 1990s, there has been a significant rise in thyroid cancer cases, with 53,990 cases predicted to occur in the United States in 2018 (Ioachimescu, 2019). According to data from the European Network of Cancer Registries, women had a three times higher incidence rate of cancer in 2012 than men (9.3 cases versus 3.1 cases per 100,000 person-years, respectively) (Filetti *et al.,* 2019). Therefore, thyroid gland disease is one of the endocrine cancers and accounts for between 1% and 1,5% of all new cancer cases diagnosed each year in the United States. Its incidence has also steadily increased globally over the past three decades (Awad *et al*., 2016).

To increase overall survival and quality of life (QoL) is the main goal of all cancer treatments. Contrary to many other cancers, thyroid cancer has a prognosis that is generally favourable. A preoperative risk assessment is used to determine the primary course of treatment for thyroid cancer patients, which usually entails surgery to lift the thyroid tissue (Ju *et al.,* 2016; Filetti *et al.,* 2019).

Longer thyroid treatments will result in significant price increases. The overall cost of thyroid treatment in the US in 2008 for females over 18 reached $4.3 billion. According to the Endocrine Society (2015), the average cost of treating thyroid disease was $343, the average cost of outpatient visits was $409, and the average cost of prescription drugs was $16.21. One study conducted in Korea discovered that the total cost of thyroid disease collected from 2002 to 2010 was 224.2 billion won in 2002, 303.4 billion won in 2004, 400.3 billion won in 2006, 570.4 billion won in 2008, and 762.2 billion won in 2010. Thyroid disease-related costs in Korea increased three and a half times between 2002 and 2010 (Hyun *et al.,* 2014).

Patients with hypothyroidism utilize medical resources and pay much higher medical costs than those with euthyroid control *(*Hepp *et al.,* 2021). The estimated annual medical costs for each patient in the United States related to hypothyroidism range from $460 to $2.555. An investigation into the cost analysis of hyperthyroid patients was carried out in one of the hospitals in Indonesia, and the breakdown of cost components was discovered. As much as Rp 42,842,900 in annual drug costs, Rp 465,683 on average per patient, or 83% of the overall cost for thyroid patients, laboratory costs make up the most significant portion of these expenses (Saharah *et al.,* 2020).

There hasn't been enough research done on the thyroid's cost of illness (C.O.I.). Policymakers and the general public can make decisions about thyroid control programs to enhance the long-term health of thyroid

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patients by using C.O.I. evaluation to understand the financial burden better. This systematic review aims to provide an overview of the financial costs associated with thyroid disease for the community, the government, and healthcare providers.

MATERIALS AND METHODS

Search strategy

The literature search was conducted on several databases: PUBMED, SCIENCE DIRECT, DOAJ, SCOPUS. The keywords used are a combination of the keywords "cost of disease", "thyroid" contained in the title or abstract of the databases. For searches in English, the keywords used are *"cost of disease", "burden of disease", "cost analysis", "cost for treatment", "thyroid disease"*. A manual search with GOOGLE SCHOLAR was also performed. Both the database search and manual search were conducted in September 2021. The literature search is restricted to articles that use either English or Indonesian.

Inclusion and exclusion criteria

Articles that meet the inclusion criteria are related to C.O.I. from various thyroid dysfunctions, both hyperthyroidism and thyroid cancer. However, for other economic evaluations besides the analysis of disease costs, for example the study of *cost effectiveness Analysis (C.E.A.), cost-benefit analysis (C.B.A.), cost utility analysis (C.U.A.)* are included in exclusion criteria. Moreover, studies that are inaccessible to the full text or only available abstracts are excluded for papers, case reports.

Data extraction and analysis

On one article will be reviewed if the same articles were obtained in the databases. The articles that have been obtained from the search results with the combination keywords of *"cost of illness", "cost analysis", "cost for treatment", "thyroid disease*", *"cost of disease"* contained in the title or abstract of the database were gathered. Then, from the results of the literature search, an evaluation was carried out to ensure that the article was relevant to the purpose of the study. Abstracts from articles obtained were then evaluated independently, and the whole text of the article was also evaluated and filtered to obtain articles that meet the research inclusion criteria. Then, the list of articles to be reviewed and data extraction was carried out. The steps in this systematic review are described in *prism flow* which maps the number of articles identified, the number of articles included and excluded as well as the reason for exclusion. In this study, quality of the research was critically evaluated following previous C.O.I. related research (Patty *et al.*, 2021). This study used a 10-point checklist; it will be given a score of 2 if all criteria were met, a score of 1 if only some criteria were met, and a score of 0 if only a few criteria were met. The maximum score was 20, with three studies of good quality, two of moderate quality and one of poor quality.

RESULTS AND DISCUSSION

Search result

Search results from the database with the keywords used resulted in 755 articles for the initial search. After identifying and removing the duplication of articles, eight articles and abstracts relevant to the study's purpose were generated. A total of three articles were then excluded because one article only displayed an abstract while the full text was unavailable. The other two articles were excluded because they belonged to C.E.A. studies. In the end, the remaining five articles met the research objectives and could be used in *a systematic review*. A manual search was also conducted on google scholar, one relevant article was obtained. Therefore, six articles were analyzed in this *systematic review* (Fig. 1).

Characteristics of the study

The six articles acquired are C.O.I. studies carried out across several nations, including Germany, Korea, Indonesia, Denmark, and the United States. The term "burden of illness" (C.O.I.), also known as "burden of disease" (B.O.D.), refers to the various ways that disease can affect how people feel about their health in a nation, particular regions, communities, and even as individuals. The C.O.I. category can include both direct and indirect costs, as well as the incidence or prevalence of a disease and its effects on age, morbidity, health status, quality of life (QoL), and financial aspects (Jo, 2014). This study focuses heavily on seeing C.O.I. from thyroid diseases with various thyroid diseases, namely *benign* and *malignant* thyroid plus hyperthyroid (n=2), *papillary thyroid cancer* (n=1), hyperthyroid (n=1), thyroid cancer plus hyperthyroid and hypothyroid (n=1), and *primary hyperparathyroidism* (n=1). These articles on the *systematic review* were published between 2002 and 2020. All studies were conducted in hospitals, inpatients, outpatients, and both. The average data collection was carried out retrospectively using medical record data, financial institution details data, SIM-RS data and insurance claim data. This study calculated the cost using the payer perspective (n=3), society (n=1) and hospital (n=2). The research characteristics of the 6 articles are shown in Table 1.

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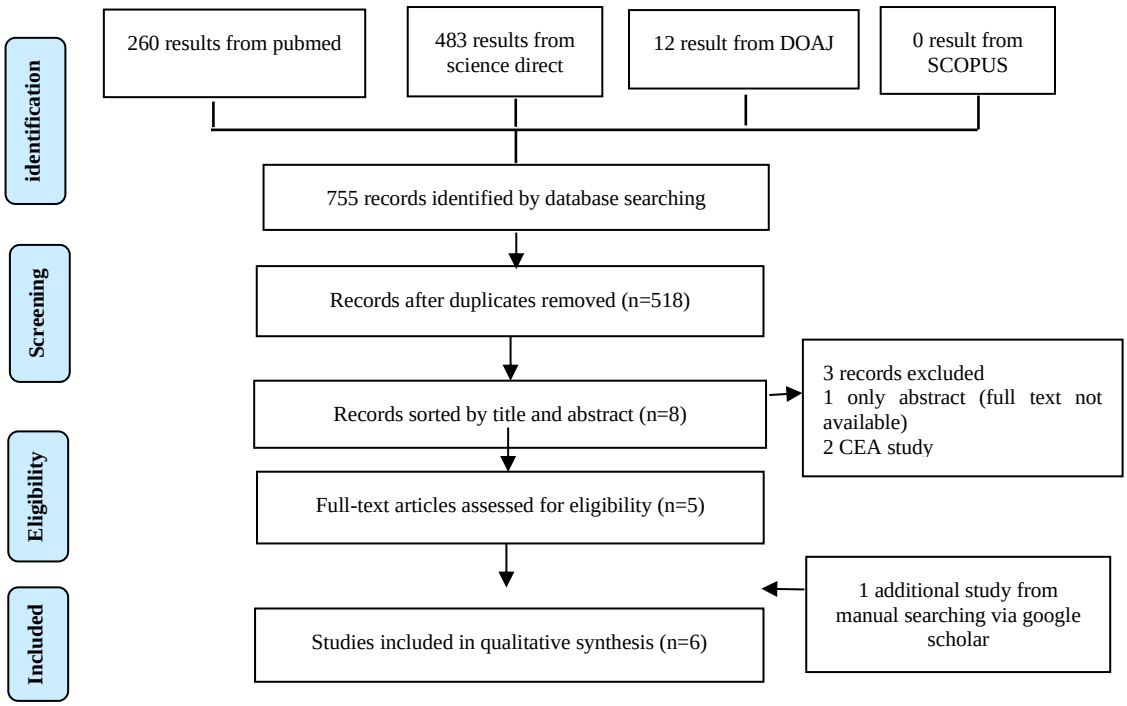

Figure 1. *Systematic review of flow diagrams*

Table 1. Characteristics of Research Articles

Authors	**City**	**Number of Samples**	**Study size**	**Epidemiological approach**	**Methods of resource qualification**	**Study period**	**Type of Disease**	**Data Source**	**Settings**	**Study design**	**Study Prespective**
Kahaly & Dietlein, 2002	Ger	5932	32 locations	Prevalence	Drummond Checklist	1981-2001	Benign and malignant thyroiditis, hyperthyroid	Cost breakdown data from insurance companies and government departments	I & O	R	P
Kim *et al*, 2018	Kor.	33	2120	Incidence	Drummond Checklist	2010-2015 (5 year periods	Papillary thyroid cancer (TPC)	Medical record data, cost breakdown data, follow-up outpatient data after surgery	I & O	R	P
Hyun *et al.*, 2014	Kor.	-	-	Incidence	Drummond Checklist	2-year intervals during the last 10 years	Malignant and benign thyroid tumors, functional abnormalities inflammation, thyroid abnormalities in newborns	Medical records, details of direct and indirect medical costs	I & O	R	S
(Saharah *et al.*, 2020	IND	92	1139	Prevalence	Drummond Checklist	January 2017 to December 2018	Hyperthyroidism	Medical record data, SIM-RS, INA-CBG package	(O)	R	H
Møllehave *et al.*, 2018	Den	100,000	5,330,119 persons	Incidence	Drummond Checklist	1995–2015 in Denmark, i.e., before and after the introduction of mandatory IF in 2000	Thyroid cancer, hypothyroidism, hyperthyroidism	Medical records data, cost breakdown data, e Danish health care system	I & O	R	P
Hollenbeak *et al.*, 2007)	US	4863	8510	Incidence	Drummond Checklist		Primary hyperparathyroidism	cost breakdown data from business departments, literature search	I & O	R	H

Note: **GER** = Germany; **KOR** = Korea; **IND** = Ind; **DEN** = Denmark; **US** = United States; **I** = Inpatient; **O** = Outpatient; **R =** Retrospective; **P** = Third party payer; **H** = Hospital; **S** = Society

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Table 2. Screening and Thyroid Surgery Cost

Authors	Screening, Thyroid surgery	Cost
Hollenbeak et al., 2007	Minimally invasive parathyroidectomy	7228 USD/patient
	Parathyroid surgery with routine preoperative thyroid ultrasonography and further thyroid treatment	8098 USD/patient
	Bilateral neck exploration (B.N.E.)	8106 USD/ patient
Kahaly & Dietlein, 2002	Lobectomy	120 USD/patient
	Subtotal unilateral thyroidectomy	88 USD/patient
	Subtotal unilateral thyroidectomy with contralateral lobectomy	96 USD/patient
	Total thyroidectomy	107 USD/patient
	Total cervical and transtoracal thyroidectomy lymphadenectomy	344 USD/patient
Kim *et al.,* 2018	Hemithyroidectomy	0.774 USD ± 0.096 USD/patient
	Total thyroidectomy	1.31 USD ± 0.187 USD/ patient
	Total thyroidectomy with R.N.D.	1.92 USD ± 0.445 USD/ Patient
	Total bilateral thyroidectomy with radical neck dissection and mediastinal dissection	21.8 USD ± 7.6 USD/ Patient

Research in various countries causes differences in costs because the currencies used are different so that a cost adjustment calculation is needed. The cost obtained in the study reviewed in this study will be converted into USD currency in 2020, where to adjust the cost must calculate *consumer price index* and *purchasing power parities*.

P.P.P.= $\frac{cost\ on\ the\ article}{PPP\ in\ 2020}$ = *Relative cost after converting to P.P.P.*

C.P.I. = Yield $\frac{CPI\ in\ 2020}{CPI\ in\ the\ year\ in\ the\ article}$ × P.P.P. = Value in USD in 2020

The consumer price index (C.P.I.) is a calculation of consumer purchasing power by looking at purchasing power in a country in various years. Whereas *Purchasing power parities (P.P.P.)* is a calculation of purchasing power by comparing purchasing power of each country by eliminating differences in price levels between countries (OECD, 2020) (BANK, 2020).

Cost of thyroid disease

The six studies showed the cost in thyroid patients with various types of diseases, namely thyroid cancer, hyperthyroid and hypothyroid. The observed costs were direct medical costs, direct non medical costs, and indirect costs for both inpatients and outpatients. Some costs were calculated from both the yearly average cost and the cost per procedure - mainly on operating procedures. The screening and thyroid surgery cost articles are shown in Table 2.

Meanwhile, a research in Indonesia conducted on hyperthyroid patients shows that an average cost for each patient per year is 125.71 USD. Unlike payments that use BPJS, the average cost of each patient is 41.68 USD per year, which is the highest cost component and is about 83%. There is a difference in cost between the hospital rate and the INA-CBGs rate of 84.03 USD per patient (Saharah *et al.*, 2020)

In some countries, the cost of surgical measures is the highest, particularly in Germany, which is around 374 USD± 120.50 USD/patient (Kahaly & Dietlein, 2002). In Korea and Denmark, the average cost of operating measures is almost the same. The average *thyroid surgery* in Denmark is 0.500 USD – 0.741 USD/per surgery (Møllehave et al., 2018). For Korea, *hemithyroidectomy* procedure costs 0.382 USD ± 0.094 USD/patient, *total* thyroidectomy costs 0.452 USD ± 0.062 USD/patient, *total thyroidectomy ipsilateral radical neck dissection* costs 0.772 USD ± 0.140 USD/patient, and t*otal thyroidectomy with bilateral*

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R.N.D. and mediastinal dissection costs 7.76 USD ± 6.67 USD/patient (Kim *et al.*, 2019)

In a study conducted in Denmark, the total cost of drugs and hospital costs for thyroid disease amounted to 12501.59 USD per 100,000 people from 1995 to 2015 (can be seen in Table 4), with an average cost of antithyroid drugs of 11.73 USD (Møllehave *et al.*, 2018). Meanwhile, in Indonesia, the average cost of drugs is 3.22 USD/patient (Saharah *et al.*, 2020). For patients treated with radioiodine in Germany anaverage of 205 USD ± 77.34 USD/patient was obtained (Kahaly & Dietlein, 2002), while for radioiodine therapy in patients in Denmark, it was 89.19 USD - 0.32 USD/patient (Møllehave *et al.*, 2018). The lowest cost is in Germany, which is around 0.125 USD/patient. While the highest cost is found in the United States, the cost of *bilateral action neck exploration (B.N.E.)* which is 8106 USD/patient. Details of thyroid treatment costs can be seen in Table 3.

Thyroid disease and disorders have a large economic impact on patients, governments and healthcare providers. Thyroid disease is more prevalent in women than in men (Endocrine Society, 2015). This study uses several perspectives in accordance with the respective research objectives, but some studies have not yet been fully conducted for non-medical and indirect costs. Systematic review related to C.O.I. in thyroid patient is still unavailable, and there is still little research. In *systematic review* not only focuses on C.O.I. from patients with hyperthyroid or hypothyroid disorders but also looks at C.O.I. in patients with thyroid cancer or other thyroid dysfunction.

The study's perspectives vary from health care providers, the government, and society. Studies from different angles, covering slightly different cost items in turn, can result in various outcomes for the same disease. The costs for a specific group are usefully disclosed by each perspective. The societal perspective is preferred because it allows a thorough analysis of all costs incurred due to the disease and is advised for potential cost analyses like C.B.A., C.E.A., and C.U.A. It is the most comprehensive because it covers all direct medical costs and indirect costs for all members of the specific society in which they are involved (Jo, 2014)

For the population groups reviewed by each study, it varies, and also in most large populations. This can affect cost differences between countries. These results can present the conditions of each country. Several studies show a long period and each data is analyzed annually to see the COI. One of the studies in this study did not mention how many total samples were analyzed, because the data was seen every two years in 2002, 2004, 2006, 2008, and 2010. The data was seen from age <19 years to >80 years where based on the age of patients 50 years had the largest portion (27.6%), then followed by 40 years (25.3%) and 30 years (18.0%) (Hyun *et al.*, 2014)

For the design study used in this *systematic review*, the average uses retrospective studies obtained from patient medical record data, patient cost detail data and also data from the insurer. This study looks at an overview of a condition or a disease. One study discussed the cost of thyroid in patients with hyperthyroidism, where the cost components measured were administration costs, doctor's consultation costs, laboratory costs, and drug costs (Saharah *et al.*, 2020). Hyperthyroidism can occur at a vulnerable age of 20-40 years because it is in fertile age with high productivity, causing anxiety, stress and depression. Hyperthyroidism has been associated with increased psychiatric morbidity; increased thyroid hormones in the blood can cause anxiety and depression (Bang *et al.*, 2014)

An important factor determining the patient's direct medical costs is the length of hospitalization (Rae H, 2013). This results in a reasonably high cost because compared to outpatients, the condition of patients in hospitalization is much more complex, requiring more examination through laboratory and doctor control costs. In addition, it is also deducted from the cost of the patient's surgical measures and the cost of the patient's medication (Kahaly & Dietlein, 2002). Surgical facility and hospital costs affect how much healthcare costs vary from country to country. Comparing the costs of treating thyroid cancer in the United States and France reveals that the former is three times more expensive than the latter, with hospital expenses and other treatment costs accounting for the majority of the difference rather than the price of the surgery itself (Finnerty *et al.*, 2014). Indirect costs also show a large cost, especially related to losing patient productivity (Kahaly & Dietlein, 2002). Treating thyroid dysfunction generates high medical costs for patients and families and can result in patients losing productivity.

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Table 3. Cost of Thyroid Disease Disorders

First Authors, Year	Year of cost estimation	Type of Disease	Total	Direct Cost	Indirect cost
Kahaly, 2002	1981-2001	Hyperthyroidism (Graves Disease)	Thyroid surgery (4631 USD) Radioiodine Therapy (5241 USD)	The cost of inpatient care in Germany is approximately 250 million/year/10,000 members (43345 USD/ patient/year)	Loss of work productivity due to thyroid disorders approximately 240 million/year/10,000 members (41624 USD/member/year)
		Toxic nodular goiter	Thyroid surgery (4186 USD) Radioiodine Therapy (4342 USD)		
		Benign and malignant thyroiditis, hyperthyroid	Average cost of Thyroid surgery 374 USD ± 120.50 USD /patient Average cost of R.A.I. 205 USD ± 77.34 USD/patient		
Kim, 2018	Data from Jan 2010 and Dec 2010 Fol 5 years 2010-2015	Papillary thyroid cancer (TPC)	Total overall cost hemithyroidectomy 0.774 USD ± 0.096 USD/patient total thyroidectomy 1.31 USD ± 0.187 USD/ patient total thyroidectomy with RND 1.92 USD ± 0.445 USD/ Patient total bilateral thyroidectomy with R.N.D. and MD. 21.8 USD ± 7.6 USD/ Patient	hemithyroidectomy (0.382 USD ± 0.094 USD/patient) total thyroidectomy (0.452 USD ± 0.062 USD/patient) total thyroidectomy with R.N.D. (0.772 USD ± 0.140 USD/patient) total bilateral thyroidectomy with R.N.D. and MD. (7.76 USD ± 6.67 USD/patient)	
Hyun, 2014	2002-2010	Malignant and benign thyroid tumors, functional abnormalities inflammation, thyroid abnormalities in newborns	2002 (301 USD) 2004 (408 USD) 2006 (537 USD) 2008 (766 USD) 2010 (1024 USD)	2002 (193 USD) 2004 (280 USD) 2006 (369 USD) 2008 (561 USD) 2010 (770 USD)	2002 (108 USD) 2004 (127 USD) 2006 (169 USD) 2008 (206 USD) 2010 (255 USD)

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Saharah, 2020	Jan 2017 - Dec 2018	Hyperthyroidism	Total Real Costs (125.71 USD/patient) INA-SBG Package (Q-5-44-0) (41.68 USD/ patient)	Laboratory 104.63 USD/patient Doctor/ patient consultation 15.58 USD/patient Drug costs 3.22 USD/patient Administration fee 2.27 USD/patient
Molehave, 2018	1995-2015	Thyroid cancer, hypothyroidism, hyperthyroidism	EUR 80,000 per 100,000 people from 1995 – 2015 (12475.20 USD/ 100,000 patients) (0.125 USD/patient)	Average cost of OAT 11.7 USD/patient/tahum The average of thyroid hormone therapy 5.5 USD/patient/year TS 0.500 USD – 0.741 USD/operation RAI 89.19 USD- 0.32 USD/ patient
Hollenbeak, 2007	1974-2004	Primary hyperparathyroidism	M.I.P. (7228 USD/patient) Parathyroid surgery with U.S. and further thyroid (8098 USD/patient) B.N.E. (8106 USD/patient)	OR ($20/minute) SI (968 USD/scan) U.S. (212 USD) F.S.P. (127 USD) Rapid testing of PTH levels ($38/test)

Description: TS = Thyroid Surgery; **RAI** = Radioiodine Therapy; RND = ipsilateral radical neck dissection; **MD** = Mediastinal dissection; **JAN** = January; **DEC** = December; fol = Follow up; **oat** = Anti thyroid drug; **MIP** = Minimally invasive parathyroidectomy; **BNE** = Bilateral neck exploration; **US** = Ultrasonography; **SI** = Sestamibi Imaging; **OR** = Operating room; **FSP** = frozen section preparation

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The number of days spent in the hospital and for outpatient visits (by sex, age, and year) for thyroid treatment is multiplied by the daily average wage (by sex, age, and year) from the Survey Report on Labor Conditions by Job Type to estimate the loss of productivity when the patient is unable to work as a result. The number of deaths (based on gender and age) is multiplied by the per capita loss from the year after the death to the year of life expectancy (based on gender and age) to determine the future income loss due to premature death (Hyun *et al.*, 2014).

This review has limitations due to differences between countries, differences in perspectives, few articles, and currency differences. This can lead to bias, and the review results cannot be generalized.

CONCLUSION

Estimating the costs associated with thyroid disease is critical to evaluation and illustration for governments and communities going forward. The study in this review illustrates the different costs in different countries; the cost of screening and thyroid surgery has the largest contribution compared to other costs. In estimating costs in each country using different methods. Treatment for thyroid patients over a long period entails increasingly high costs. It is evident in a financial burden that continues to increase from year to year in some countries. This has an impact on society, especially social impacts and economic impacts. The analysis related to the cost burden of thyroid patients in the future must be carried out in order to be able to estimate the cost of more specific therapies in order to provide useful data for health care providers, the government and the community.

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