

Thesis work

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**Health economic evaluation of cancer costs in the MENA region:
A systematic review and costs transferability analysis among
countries.**

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MSc in Health Policy, Planning and Financing 2021

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Abstract

Objective: Taking into consideration the increasing burden of cancer on one hand, and the limited healthcare resources in the Middle East and North Africa (MENA) region on the other, this research aims to evaluate the methodological quality of cancer health economic evaluation and assessing the quality of cancer costs reporting in the region, to explore the potentials for transferability of retrieved cancer costs within the region, and how they can be utilized to enhance evidence-based oncology decisions and future research in the MENA. **Methods:** First, a systematic literature review was conducted to obtain all health economic evaluation studies from the region between the years 1995 and 2019, following the PRISMA guidelines. Eligible studies from previous systematic reviews from MENA were also included. Then all cancer health economic evaluations were identified and reviewed, the reporting quality of certain studies was appraised using the CHEERS guidelines, and common cancer costs among the countries were first adjusted to 2020 value, then explored through comparative regression analysis to assesses their quality and identify the key parameters that drive their heterogeneity. **Results:** From 1646 citations of full-text English articles and four systematic reviews, 206 eligible papers reporting healthcare costs from the MENA region were identified. Out of these, 18 cancer health economic publications were found, reporting 260 cancer costs between the years 2007 and 2019. Appraising the five cervical cancer studies' quality, using CHEERS checklist, showed relatively good scores. 5 common costs were found among these studies, which is the annual cost of cervical cancer management per woman. The mean for these 5 costs after the adjustment to the base year (2020) was 3244.52 USD. In the regression analysis, neither GDP, nor time, nor reporting quality, nor reported treatment components explained variance in the costs among the countries. **Conclusion:** In order to provide policymakers and stakeholders of the region with more reliable and comparable cancer cost data, it's vital at this stage to enforce the role of health economic evaluation and standardize the economic methods when estimating healthcare resources. Finally, when transferring costs among jurisdictions of the MENA region, it's recommended to take the average of the same cancer cost that was already reported in different countries within the MENA, and estimating the new cost using sensitivity analysis and a certain standard deviation, rather than relying only on the estimates of one country as it was done by previous studies. The validity of this method has been evaluated using the 5 available cervical cancer studies as a benchmark.

Key words: health economics, cancer costs, Middle East and North Africa, cervical cancer, transferability, cost-effectiveness analysis, health economic evaluation.

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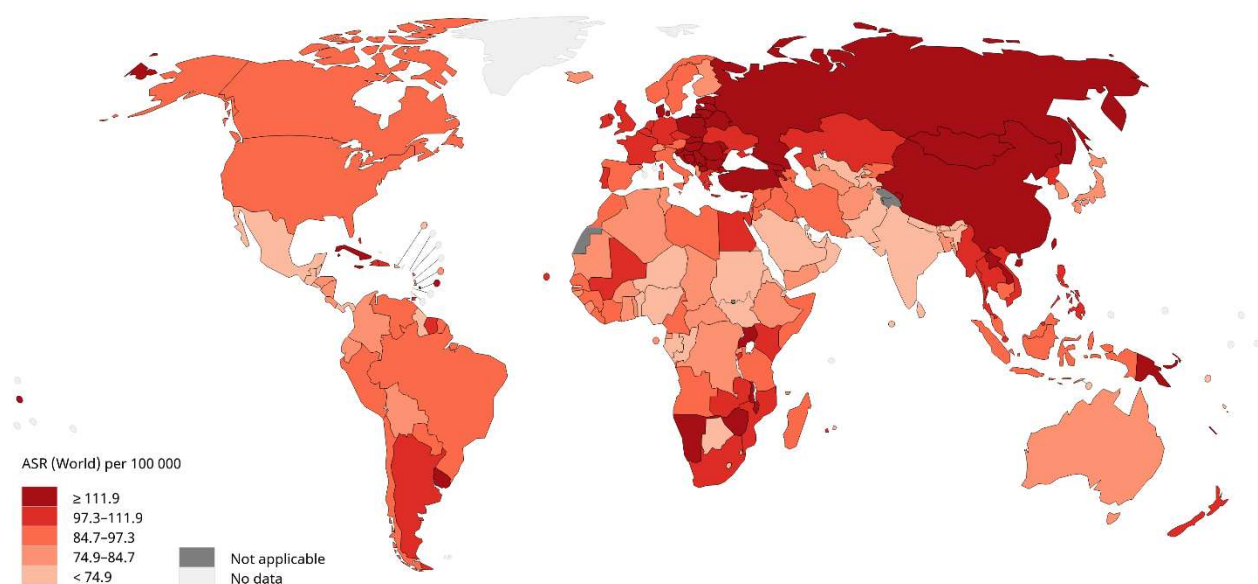
1. Introduction

1.1 Global Cancer Burden

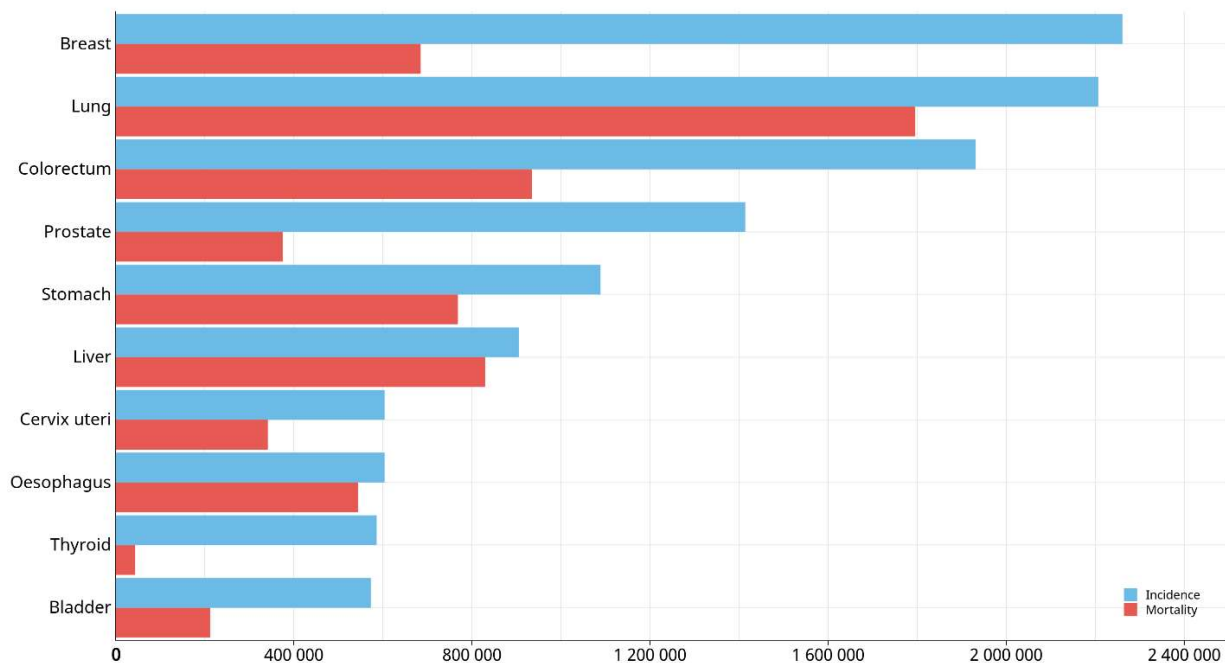
Cancer is continuing to be one of the leading causes of non-communicable diseases (NCDs) deaths around the world, provoking more than 4.5 million global premature deaths. One out of six deaths globally is due to cancer, moreover, it's the first or the second main reason behind premature deaths in 134 countries around the world.

The prevalence, incidence, and mortality rates of cancer are still rising in distressing rates due to increased life expectancy, the aging population, risky behaviors, and other demographic and epidemiological attributes. In 2020, the world witnessed 19.3 million new cancer cases, 9.96 million cancer deaths, and more than 50 million cancer cases with a 5-year prevalence. Researches showed alarming predictions, that unless proper measures have been employed to control this disease, by 2040, cancer incidence will reach 37 million new cases by year.

Around 11.7% of the new 19.3 million cancer cases globally in 2020 were breast cancer, followed by lung cancer 11.4%, colorectal cancer 10%, prostate cancer 7.3%, and stomach cancer 5.6%. On the other hand, lung cancer was the primary cause of cancer deaths around the world; 18% of all deaths, followed by 9.4% colorectal cancer, 8.3% liver cancer, 7.7% stomach cancer, and 6.9% breast cancer caused mortalities.



Graph (1): Estimated age-standardized mortality rates in the world in 2020, all cancer types, both sexes and all ages. (Data source: GLOBOCAN 2020 Graph production: IARC (<http://gco.iarc.fr/today>) World Health Organization).



Graph (2): Estimated number of incident cases and deaths worldwide in both sexes in all ages in 2020.

(Data source: GLOBOCAN 2020 Graph production: IARC (<http://gco.iarc.fr/today>) World Health Organization).

Cancer also comes with financial hardships, catastrophic payments, and loss of employment for both the patients and their family members who provide supportive unpaid care, affecting countries' economies drastically due to premature deaths and lost productivity. For instance, in 2009, around 945 million euros have been lost in Europe due to cancer premature deaths. ("WHO report on cancer: setting priorities, investing wisely and providing care for all", 2021). Trends towards greater consumption of health care services and the constantly increasing costs of cancer care are expected to push the economic burden of cancer to a further extent. (Yabroff, Lund, Kepka & Mariotto, 2011). Additionally, the poor mental and physical health and the emotional distress related to the disease might all contribute to increased cancer mortality rates. Estimating the real economic impact of cancer that includes healthcare expenditure and productivity loss of patient's morbidity and their families is becoming highly important for the decision-makers in healthcare systems and the whole society. (Yabroff, Lund, Kepka & Mariotto, 2011).

While high-income countries are witnessing progress in positive trends of cancer incidence and mortality, as a result of cancer control programs and policies, low and middle-income countries are still lagging behind. More than 60% of low-income countries have either limited or no capacity to implement the necessary cancer prevention and management measures.

Social and economic factors are major contributing factors to cancer incidence and mortality rates and how drastic is the economic burden of the disease. Socioeconomic factors such as education, employment, income, and health literacy can lead to unequal and inadequate access to treatments and cancer prevention programs, especially in lower-income countries. For example, in 2014, up to 34% of young women living in high-income countries have received the human papillomavirus (HPV) vaccine, protecting them against the main cause of cervical cancer, while only 3% of their counterparts in low to middle-income countries received the vaccination. ("WHO report on cancer: setting priorities, investing wisely and providing care for all", 2021).

1.2 Cancer Burden in the MENA Region

The Middle East and North African region (MENA) face many challenges when it comes to cancer management, prevention, implementing treatment strategies, obtaining accurate population data, and acquiring reliable information which is due to various reasons including the scarce financial and manpower resources, the limited technical capacity and the ongoing migration crisis and political conflicts. (Znaor et al., 2018)

The MENA region, which has broad definitions on the basis of which countries are included, is made up of 22 countries in the Middle East and North Africa as in the most popular and widely used definition including the WHO, with an estimated population of 676 million representing almost 9% of the world's population. The region is prominently characterized by its heterogeneity with respect to historical background, ethnicity, and sociodemographic profiles. The MENA is also not homogenous in terms of economic structure, including low, middle, and high-income countries, with different population health outcomes, different levels of health expenditure, and varying health care infrastructure. Table (1) summarizes some of the main socio-economic indicators of some of the countries in the MENA.

Many countries in the Region are experiencing serious hurdles in running efficient and well-functioning health systems in order to provide their population with equal and quality services without financial burden. These challenges include inadequate health funding, weak governance, and administration, shortage of trained health workforces, the imbalanced geographical distribution of healthcare resources, and suboptimal quality of health care. Safety and security for providing health services in conflict zones such as Syria and Yemen is also a major concern. The wars and social and political conflicts have led to the forced displacement and migration of

millions of people, disturbing the function and efficiency of health systems furthermore and putting more strain on healthcare resources. For example, in 2018, 1 in 6 people in Lebanon, and 1 in 14 people in Jordan (or 72 per 1000) were refugees. (WHO Regional Office for the Eastern Mediterranean, 2020)

Country	Population in 2019	GDP per capita (current US\$) in 2019	Health expenditure (% of GDP) in 2018	Total life expectancy at birth in 2018	Fertility rate, total (births per woman) in 2018	Death, by non-communicable diseases (% of total) 2019
Algeria	43,053,054	3974.0	6.22	77	3.0	79
Bahrain	1,641,172	23504.0	4.13	77	2.0	86
Egypt	100,388,073	3019.2	4.95	72	3.3	86
Iraq	39,309,783	5955.1	4.11	70	3.7	67
Jordan	10,101,694	4405.5	7.79	74	2.8	80
Kuwait	4,207,083	32000.4	5.00	75	2.1	79
Lebanon	6,855,713	7583.7	8.35	79	2.1	89
Libya	6,777,452	7685.9	6.05	73	2.2	75
Morocco	36,471,769	3204.1	5.31	76	2.4	84
Oman	4,974,986	15343.1	4.13	78	2.9	80
Palestine	4,685,306	3562.3*	9.80	74	3.6	77*
Qatar	2,832,067	62088.1	2.49	80	1.9	77
Saudi Arabia	34,268,528	23139.8	6.36	75	2.3	73
Syria	17,070,135	2032.6**	3.57	72	2.8	75
Tunisia	11,694,719	3317.5	7.29	77	2.2	86
UAE	9,770,529	43103.3	4.23	78	1.4	77
Yemen	29,161,922	774.3	4.88	66	3.8	50

Table (1): Socio-economic indicators for selected MENA countries. *2018 data. **2007 data.

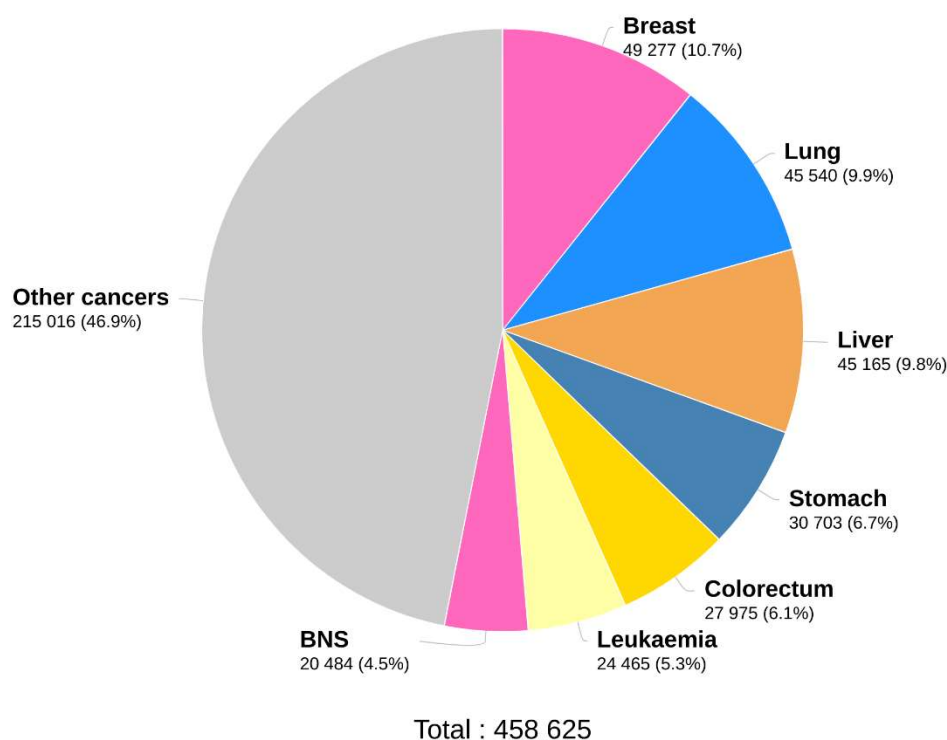
(Data source: The World Bank, Data <https://data.worldbank.org/indicator>).

The aging population of the MENA and the increasing unhealthy lifestyle behaviors are shifting the region toward an epidemiological transition from communicable diseases to NCDs, like the rest of the world. Cancer is one of the four main leading causes of NCDs-related deaths in the region. And in the next decade, the MENA is expected to witness the highest cancer burden in the world. (Lyons, Sankaranarayanan, Millar & Slama, 2018)

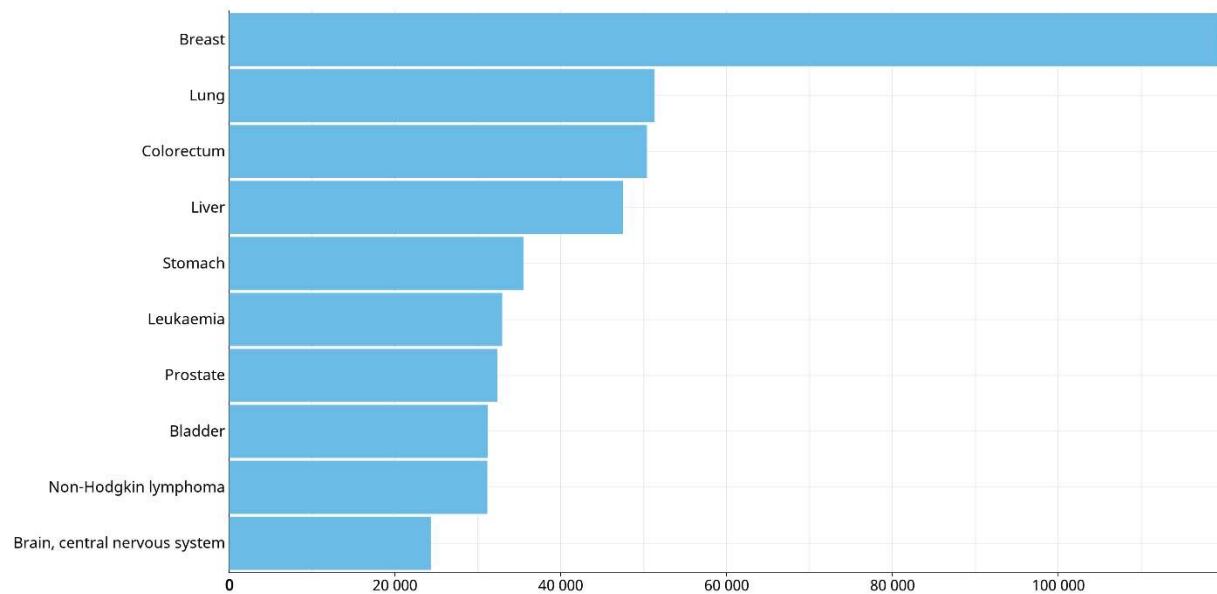
According to Cancer Today, a data visualization tool for exploring the global cancer burden in 2020 by the International Agency for Research on Cancer, over 733,965 new cancer cases and

458,625 cancer deaths occurred in the MENA region in 2020. Breast cancer was the leading cause of cancer mortality in 2020 (49,277 deaths) in the Region, followed by lung cancer (45,540 deaths) and liver cancer (45,165 deaths) as observed in Graph (3). Breast cancer had also the highest estimated number of new cases among MENA countries, except for Egypt where the number of new liver cancer incident cases was the highest. This high incidence of liver cancer in Egypt is due to the country's high historical prevalence of hepatitis C virus infection.

Cancer survival rates are relatively low in the region when compared to rates in Europe and the United States. For example, the MENA region has a cancer death per 1.5 cancer cases, whereas, in the US, the rate is one cancer death for every 2.2 people diagnosed. This is mainly due to the fact that many patients tend to be diagnosed at a very late incurable stage of the disease. (Lyons, Sankaranarayanan, Millar & Slama, 2018)



Graph (3): Estimated number of cancer deaths in the WHO East Mediterranean (EMRO) region, in both sexes, all ages in 2020. (Data source: GLOBOCAN 2020 Graph production: IARC (<http://gco.iarc.fr/today>) World Health Organization).



Graph (4): Estimated number of cancer incident cases in the WHO East Mediterranean region (EMRO), in both sexes, all ages in 2020. (Data source: GLOBOCAN 2020 Graph production: IARC (<http://gco.iarc.fr/today>) World Health Organization).

With the increasing adoption of the western lifestyle, high obesity, and lack of physical activities especially among the population in the GULF countries (Bahrain, The United Arab Emirates, Oman, Qatar, Kuwait, and Saudi Arabia), cancer incidence rates are expected to multiply in the near future. (Znaor et al., 2018). Model figures suggest that the cancer incidence rates in the MENA region will almost reach 961,000 new annual cases by the year 2030. This increase in cancer cases is mostly due to the growing population, increasing life expectancy, and risky lifestyle behaviors, including poor diet, lack of physical activity, and heavy tobacco use.

1.3 Cancer Care in the MENA Region

Despite these alarming rates and trends, there is a serious shortfall in cancer management in the Region. Only half of the MENA countries have taken the proper measures to control cancer including having approved treatment and referral guidelines (Lyons, Sankaranarayanan, Millar & Slama, 2018). And there's a tendency to focus more on screening strategies rather than focusing on early diagnosis for early detection.

The region suffers from a lack of financial and manpower resources in the healthcare sector, such as specialist surgeons, oncologists, and multi-disciplinary teams, besides the very limited access to some medicines, specialized surgeries, and cancer management technologies Moreover, the

access to cancer treatments is substantially variable among MENA countries which is the consequence of inadequate funding resources, insufficient staff training programs, political conflicts, and economic instabilities. (Lyons, Sankaranarayanan, Millar & Slama, 2018).

Cancer drugs, pathology services, surgeries, and subsidized chemotherapy availability is a challenge for several low-income countries in the region such as Sudan and Yemen. And despite that cancer drugs and some interventions are free for patients in most of the MENA countries, the access varies massively based on the country's income and development level. For example, radiotherapy equipment which can cover up to two-thirds of the region's needs is limited in certain countries in the region. Surgical interventions are available in more than 70% of the region, however, specialized surgeries are only available in middle to high-income countries. And while some countries have specialized surgeries and surgical units and staff for each cancer type, other countries have the same medical staff performing all cancer surgeries. Access to pain relief medications is restricted in many countries, due to overly strict legislation, limitations of oral medications especially oral opioids, and lack of supply and distribution policies.

In 2005, due to the scarce resources in all the MENA countries, it was proposed by the world health organization (WHO) to set up a National Cancer Control Committee to manage the region situation to the best use of interventions, treatments, and use of resources, however, the progress is still slow till this date. Only 8 countries in the region had implemented cancer control policies, and three countries had partially set up a cancer strategy. Some countries such as Jordan and Oman had already incorporated multidisciplinary teams (MDTs) including pathology, radiology, and surgical specialties for effective cancer management, while other countries are still behind, lacking treatment guidelines and diagnostic facilities.

Only half of the MENA countries, which are the high-income to upper-middle-income countries have approved cancer treatment guidelines. In contrast, only 17% of the low-income countries have approved cancer management guidelines and they lack any protocols for post-diagnosis referrals. Except for few countries, palliative care is available at an early stage of development and not properly integrated within the public health system, leading to many challenges within the areas of governance, human resources, and medication availability for palliative care. Most of the population lacks the proper understanding of palliative care services. Many healthcare staff have

not undertaken any sufficient palliative care training and there is a lack of specialist palliative care professionals.

Early detection is one of the key elements in cancer control when patients have higher survival rates. To make sure that early detection is effective, the rapid identification of symptoms, and prompt referral must be insured once cancer is clinically suspected and integrated into primary care. However, early detection of cancer is limited mostly in MENA low and middle-income countries.

For instance, early diagnosis in breast cancer, which is the most common cancer in the region can improve survival rates massively. Jordan and Morocco are great examples of low and middle-income countries which had successfully scaled up breast cancer early detection. In Jordan, breast cancer survival and early diagnosis rates due to increased education and awareness campaigns, leading to a decrease in the proportion of stage III diagnoses from 56% to 23% between 2005 and 2009. Similarly, a nationwide awareness campaign and proper medical staff training in Morocco led to an increased early-stage diagnosis of breast cancer. While in Qatar and Saudi Arabia, the ineffectiveness of breast screening services is due to low population awareness and inadequate participation in the screening program. (Lyons, Sankaranarayanan, Millar & Slama, 2018)

It's also noted that the access to vital cancer data in this region is either constricted or the data is of low quality, despite that some data such as mortality, prevalence, and costs are crucial indicators of the actual disease burden and it's fundamental when estimating cancer incidence and survival rates. The country's stage of development is highly linked with more developed cancer management and surveillance policies, as countries with a higher Human Development Index (HDI) tend to have better oncology management infrastructure.

The ongoing migrations, political instability, and low governmental capabilities in the MENA region are making cancer care, management, and monitoring more and more challenging. The cost of these challenges is high, especially with the wide adoption of western lifestyle habits and the aging population leading to rising cancer rates. The lack of availability and low quality of cancer data in the MENA can also be the result of some traditions and customs in the region such as rapid burial tradition which is common in most of these Arabic countries and limited reliance on patient records. Some of these countries such as Qatar, Saudi Arabia, and the United Arab Emirates have

started already the utilization of health information systems, but the quality assessment of the generated data has not been done yet. (Znaor et al., 2018)

National and international stakeholders should collaborate in order to strengthen the capacity of cancer control, early diagnosis, and prevention in the MENA region. Implementing frameworks that promote public awareness of cancer symptoms, training health professional on early cancer detection and specialized treatments, investing in cost-effective cancer care and management, and better surveillance and monitoring of cancer data are needed to lower cancer mortality and incidence rates, reduce the economic burden of cancer and generating a better quality of life for patients in the MENA countries while taking in consideration the different settings of each country to ensure the most cost-effective use of the limited budget and scarce resources. (Lyons, Sankaranarayanan, Millar & Slama, 2018)

1.4 Research Objective and Question

Within this scope of insufficient accessibility and availability of cancer treatments, the lack of health technology assessment, and the limited integrated protocols for managing this disease, it's vital at this stage that every single cancer financing decision in the MENA regions is based on economic evidence, ensuring the best allocation of the scarce resources, particularly in settings affected the most by conflict and instability. Furthermore, the lack of protocols and varying access to treatments increases the heterogeneity of real-life treatment practices, limiting the transferability of cost and outcome data between jurisdictions, and even between health service providers for the purpose of health economic evaluations.

Therefore, the goal of this research will be exploring the quality and potential for transferability of regionally reported cancer healthcare costs, by systematically reviewing health economic evaluation publications; including cancer studies in the Middle East and North Africa (MENA) countries between the period of 1995 and 2019, and assessing the methodological and comprehensiveness of these health economic studies followed by assessment of the quality of the retrieved cancer costs to understand in which context they were used and on which therapeutic and diagnostic oncology protocols they were based.

According to the findings, this study can decide on how sufficient is the cancer health economic evaluation in the MENA region and proposing practical recommendations for better reporting and evaluation of cancer health costs in the MENA, based on our assessment and considering the

variation in the economic and epidemiological states of the countries. Moreover, taking into account the limited availability of cancer cost data in the region, this research will examine the potentials of identifying a set of critical factors for the methodological and transferability analysis for utilizing these already found and published cancer costs in further studies for the purpose of saving time and resources spent on health economic research in the region, while providing reliable estimates for evidence-based oncology decisions and policies in the MENA health systems.

Based on the above considerations, the research has three questions to answer, which are:

“1) What is the methodological quality and comprehensiveness of cancer health economic evaluation and costs reporting in the MENA region? 2) What are the key parameter inputs that drive the heterogeneity in cancer costs among these countries? 3) And what’s their impact on the potential transferability of these costs?”.

1.5 Thesis Structure

This research is divided into five chapters, with the following brief outline:

*Chapter 1. **Introduction:*** The first chapter comprises an introduction on the burden of cancer both globally and in the MENA region and what led to the development of the research question and objective.

*Chapter 2. **Theoretical Review:*** In this chapter theoretical review and empirical findings on health economic evaluation generally and in cancer specifically from the existing literature is presented and discussed.

*Chapter 3. **Research Methodology:*** This chapter presents the research methods in literature search, study selection, data extraction and management, and the steps of quality assessment and adjustment of the cancer costs.

*Chapter 4. **Results and Analysis:*** All the findings of the systematic review from the selected studies to the descriptive analysis and the results of the costs quality assessment and regression analysis.

*Chapter 5. **Conclusions:*** The last chapter includes the general conclusion and general discussion of this research finding as well as limitations and the recommended further research.

2. Theoretical review

2.1 Health Economics and Health Economic Evaluation

Health economics is one of the applications of economic theories that covers a wide range of issues from micro-evaluation of medical interventions to analytical techniques in managing scarce resources to producing better health outcomes. It's vital for offering a framework for examining the most important public health issues and identifying possible solutions to tackle them. Moreover, health economics is essential for informing the decision-makers as in governments, providers, and other healthcare stakeholders, on how and which healthcare should be funded, provided, and distributed while making the most out of the available money and resources.

Furthermore, health systems are massive components for the spending and investment of many countries all over the world, thus the economic performance of these systems is an important element in the world's overall economy. And as health systems are constantly and rapidly changing, it's important that policy and decision-makers emphasize their focus on finding better ways for delivering health care services, that suits the public demand of healthcare, while taking into consideration other factors such as access barriers, lifestyle choices, patient demographics and other socioeconomic factors that determine the demand for healthcare.

This is why health economic evaluation is highly needed, where it explores the different utilization of health resources when new health intervention is introduced. It's a great tool for stakeholders to acquire information when implementing healthcare decisions, for health insurers to decide which service they should reimburse, and for the government on how to allocate healthcare resources. It provides a comparative analysis between alternating medical interventions to the same health issue in terms of the value of their inputs and outputs, in order to identify on which, the resources should be utilized and what would be the opportunity cost of financing one alternative over the other, from the viewpoint of individual, community, or society. (Dewar, 2017)

2.2 Healthcare Costing

Healthcare costing can consume lots of time and effort and might not turn out to be as perfect and accurate as it should be every time, and decision-makers need to come up with judgment of how precise the cost estimates need to be within a given study.

One of the most precise costing methods is based on micro-costing, while the least precise methods are the ones based on daily costs (average per diems). Different levels of accuracy can also be applied to different cost items. (Drummond, Sculpher, Claxton, Stoddart & Torrance, 2015). For

example, in cancer costing, laboratory tests that cost only a few cents are not worthy of accurate cost investment, while other costs such as surgeries and radiotherapy can constitute a major component of cancer care costs, and therefore requires more accuracy when estimated.

And where total patient costs are usually calculated by summing all resource costs consumed by the patient during the treatment, the mean total cost of an intervention is calculated by dividing the sum of all individual patient total costs by the total number of patients included in the analysis.

Also, when conducting economic evaluations, all future costs need to be discounted using discount rates between 3% and 5%, due to time preference where the dollar today is worth more than a dollar in the future in addition to the opportunity cost of spending this money at the present instead of the future. (Smith & Rudmik, 2013)

Some deficiencies might exist in estimating both quantities and prices when identifying the year of costs retrieval or even when specifying the study perspective. Therefore, utilizing economic evaluations would be wise in subjecting costing methods to a fair degree of scrutiny, where all studies state clearly the methods and sources used in estimating the quantities and prices when calculating the costs. (Drummond, Sculpher, Claxton, Stoddart & Torrance, 2015). Having standardized cost reporting and increasing the quality of economic evaluation is critical to improving the transparency of methods, and for decision-makers to be able to make fully informed and accurate decisions regarding resource allocation. (Smith & Rudmik, 2013)

When using already available cost data, it's important to assess at first how were these cost estimates derived, what categories of costs do they include, and how relevant and up-to-date are these estimates now. For example, simple inflation in the cost of a medical intervention that had some dramatic technological changes and advances that resulted in the change of the whole treatment cost, won't be sufficient. Moreover, when calculating the total cost which requires multiplying the quantities of resources by the unit costs (prices) of those resources, the level of precision of the estimation of these resources should be considered to match the level of details in the total costs that are needed, or vice versa. (Drummond, Sculpher, Claxton, Stoddart & Torrance, 2015)

Statistical tests and sensitivity analysis are important in handling cost uncertainties that might be caused by the imperfection in research data, and they are vital components to all economic evaluations. Most of the uncertainties in healthcare costing arise from the resource valuation

(prices determination), quantifying the consumed resources, or from the discounting rates. And since cost data might have imperfections, the determination of how robust the results of economic evaluation in the face of changing data is necessary. Sensitivity analysis, which is a probabilistic analysis where key variables for both costs and effects are altered and the changes to final outcomes are evaluated. Although there are several forms of sensitivity analysis, it is still considered the most robust and comprehensive method of handling uncertainty in economic evaluations. (Smith & Rudmik, 2013)

Key terms and methods in healthcare costing	
Micro-costing	It's a method that allows precision in costing healthcare resources, by estimating the cost of every component of the services consumed (e.g. laboratory tests, hospital days, drugs) and deriving a unit cost for each as accurately as possible.
Average per diem (daily cost)	The average of the per diem of all types of patients.
Disease-specific per diem (or daily cost)	The average of daily costs of management and treatment of a specific disease area which is a broad term that includes several diseases.
Direct healthcare costs	Costs that are directly incurred by the medical management of the disease and patient care such as drugs, medical supplies, operations, hospitalization, diagnosis, physical rehabilitation, outpatient visits and etc. It also includes capital and health labor costs.
Direct non-healthcare costs	All the expenses incurred by the illness that does not include the direct consumption of medical service. Such as travel expenses and home renovations.
Indirect costs	Indirect health costs are all the nonmedical management costs incurred by productivity losses, lost wages, and informal care within the course of illness that would have otherwise not been incurred.

Costs Discounting	Discounting is the reflection of differential timing of costs of certain courses of actions under consideration, over multiple timespans, as people usually tend to value benefits at the present time higher than what they would do in the future. When performing economic evaluation studies, all future costs need to be discounted to reflect the change of dollar value which worth more today than in the future, using a discount rate that is usually between 3% and 5%. Discounting also represents the opportunity cost of investing the money and resources at the present instead of the future and expressing the costs in their current value.
Discount Rate (r)	The discount rate reflects what would be the social rate of time preference and expresses it in present value instead of the future periods, and what would people prefer now for their own benefits rather in the future. The official discount rate is might be determined by official guidelines for economic evaluation in the jurisdictions where the studies are conducted. Otherwise, the discount rate is typical, between 3-5% per annum, to allow comparison among different analyses, and it's usually the same rate that is used to discount benefits in the existing literature.
Sensitivity Analysis	Sensitivity analysis which is becoming a necessary tool in health economic evaluation is meant to determine the means of the robustness of the economic evaluation when the estimates might bear uncertainty under controversial circumstances. It identifies the uncertainty of estimates in a study and how they are likely to impact the results of the study. Sensitivity analysis is used when there's a variation in the data collection or measurement, controversial judgments in the value such as the discounting rate, or when new variables are being used. Additionally, it helps to show the conditions that would make the course of action inefficient relative to other alternatives. The basic approach in sensitivity analysis is setting an expected upper and lower ranges of the estimates which can be collected from evidence from other research and practices, based on varying the parameters in question.

Table (2): Some key terms and methods used in health economic evaluation

2.3 Transferability

However, the results of health economic evaluation might vary among different places due to different health care resources, varying clinical and treatment practices and parameters, and different prices and costs, which call for customizing health economic analysis for each setting in each country, while keeping in mind the data availability and the decision-makers requirements.

Cost data and economic evaluation results could be transferable if they can be adapted to other settings. The availability of data plays a key role in determining whether cost-effectiveness results are transferable between different settings. Assessing whether the results of an existing economic evaluation are transferable and can be adapted in a certain setting would be of great use rather than developing a new economic evaluation. Accordingly, the main goal here would be how the results of health economic evaluation can be adjusted to become transferable to another setting. (Drummond et al., 2009)

For starters, the healthcare intervention or the comparators have to be relevant to the setting or the country of interest, in addition to the patient population which has to be similar. Another important aspect would be the methodological quality of cost which has to meet the standards of the new setting. Otherwise, the results of the economic evaluation won't be transferable between the original and the new setting. Furthermore, the results would be transferable after performing the necessary adjustments on the treatment pattern, unit costs, and other factors. For instance, unit costs might be recalculated in order to become transferable to the new setting or just have some simple adjustments for example based on purchasing power parity. Time horizon, the perspective of the health economic evaluation, the discount rate applied, type of cost and if the indirect costs such as productivity losses were included, and how they were valued should also be considered when examining if the data is transferable or not.

Also, whether there's evidence of heterogeneity between countries/settings of interest in terms of resource use, costs, patient demographics, and utilities should be analyzed. In general, health economic research should focus on the next step into understanding the sources of local differences that affect economic data transferability, and whether certain countries with similar settings can be grouped together for the purpose of analyzing health economic data transferability. Health economists should also consider issues that stand in the way of data transferability when conducting cost-effectiveness analysis and other economic evaluations. (Drummond et al., 2009)

2.4 Cancer Costing

The increasing volume of cancer health care services consumption with the rising costs is expected to push the burden of cancer worldwide to further limits. Consequently, estimating the economic burden of cancer including direct and non-direct medical costs and the productivity loss of the patients and their families is highly important for healthcare systems and stakeholders.

For investigating the economic burden of disease, both the value of the consumed resources when treating the disease and the loss of opportunities caused by cancer should be measured. The value of resources used (direct medical costs) can vary for cancer patients according to the stage and site of cancer. Estimating and utilization of cancer costs is typically done by comparing individuals without cancer with cancer patients through matching their individual characteristics, such as age and sex, where the difference is measured as a “net cost” or in statistical modeling. This approach is used since it’s difficult to estimate some specific healthcare services for cancer when compared to other morbidities. (Barlow, 2009)

Cancer costs can be either reported as Incidence costs when reported from the time of diagnosis typically reported starting at diagnosis or on the time of a specific event for a cancer patient group, or as prevalence costs when reported for all cancer survivors alive in a specific year. Both forms of reporting can be highly useful for policymakers. And while incidence costs are utilized more in comparing treatments in cost-effectiveness models, prevalence costs are used more in analyzing the overall impact of cancer on local or global health plan budgets. (Yabroff, Lund, Kepka & Mariotto, 2011)

Prevalence costs which include the costs for specific cancer diagnosed population over a fixed calendar time period are of great interest to healthcare payers and policymakers when planning healthcare expenditure. Accordingly, the cost proportion of each cancer phase (newly diagnosed, survivor, or terminally ill) in any specific cancer is variant according to the population at risk and treatment effectiveness. However, the consequences and effects of cancer prevention strategies or treatment might be difficult to detect through prevalent costs since it only reflects the impact on the incidence of cancer or immediate treatment costs. On the other hand, incidence cancer costs represent the costs from the time of diagnosis and from an individual perspective and it’s useful when analyzing the effect of treatment interventions and strategies. (Barlow, 2009)

Using different data sources when estimating the medical costs that cover patient populations, payers, and types of services could lead to different cancer cost estimates. Therefore, a head-to-head comparison of the different costing methods and data sources used when estimating cancer costs among different studies and countries, while having the same standard study criteria, patient samples and definitions will inform the combination of estimates across data sources and populations. (Yabroff, Lund, Kepka & Mariotto, 2011). Additionally, having a standardized

definition and method among MENA countries' health care systems will also enhance understanding of the role of health systems and the cancer care delivery on the burden of cancer.

Cancer can lead to lower employment opportunities for diagnosed patients, and possibly to a loss of health insurance. It might also influence the employment for cancer caregivers through Informal caregiving, especially when the patient is a child, limiting both the patient and the caregiver from holding a full-time job due to high rates of absenteeism when traveling or waiting to receive specialized cancer care or when giving informal care. (Yabroff, Lund, Kepka & Mariotto, 2011)

Indirect costs of cancer include the monetary losses as a consequence of the time spent waiting or traveling to receive cancer care (time costs), lost time at work due to illness such as going to clinical visits, taking medical tests, taking days off while still being employed (absenteeism) or loss of productivity during working hours due to working with pain or disabilities (presentism), in addition to the loss of productivity caused by informal care. Cancer informal care is expected to grow more due to the aging population and increased life expectancy after diagnosis with advanced screening, treatment, and detection technologies. Estimates of indirect cancer costs that cover all individuals and all aspects including patients and caregiver lost productivity, time costs, and mortality costs are extremely important to be included. Exclusion of indirect medical costs of cancer from economic evaluation, especially in cost-effectiveness analysis might lead to bias toward underestimating the costs of cancer and some cancer treatment that put a higher burden on cancer patients and formal caregivers. (Yabroff, Lund, Kepka & Mariotto, 2011)

Also, having specific cancer cost estimates according to the cancer site, or treatment type is useful in cost-effectiveness models when comparing different treatments, or when budgeting the healthcare plan and assessing the equity of cancer care. It's also essential to consider the demographic and tumor characteristics of the patients that can directly affect the cancer care costs. Finally, as cancer care costs may extend for several years after the point of diagnosis, these costs should be discounted or inflated with specific rates, and probably adjusted to a common time frame when combined from several years. (Barlow, 2009)

2.5 Health Economic in the MENA Region

The MENA Region which hold diverse countries in terms of geographic and demographic characteristics, economic performance, and standards of living, has witnessed recently new developments when it comes to the healthcare reforms in the region toward more value-based

decisions in healthcare. A number of pharmaeconomic guidelines have been already published in both high- and middle-income countries in the region.

However, the region is still behind when it comes to the quality and quantity of health economic research and when managing the scarce data and resources. (Zrubka, Rashdan & Gulácsi, 2020). Health Technology Assessment (HTA) which is the assessment of properties and effects of a health technology and evaluation of the direct and intended effects of this technology and what might be the indirect and unintended consequences done by interdisciplinary groups that use explicit analytical frameworks drawing on a variety of methods, is becoming more important for the MENA region to support health policy decisions for both increasing the return on investment and budgeting the healthcare expenditure. However, the main core components of HTA, especially economic evidence is still not applied enough in pricing and reimbursement decisions of health technologies. The implementation of health technology assessment which can be categorized in the region as highly heterogeneous among the countries with very limited funding, is still in a very early stage. (Fasseeh et al., 2020). The same for health economic evaluation research which is still a new concept to the region.

Considering the increasing burden of cancer in the region, the limited availability of cancer cost data, and the increasingly important role of health economic research in informing decision maker of how to make the best of the available resources and allocate them efficiently where it's needed the most, It's important at this stage to explore the critical factors of cancer health economic evaluation and the methodological quality of reporting cancer costs in the MENA region to ensure that both time and resources are saved when conducting future health economic research while providing reliable cost estimates for implementing cancer treatment and prevention policies.

3. Research Methodology

3.1 Systematic Review of Health Economic Evaluations Including Cancer Studies from the MENA Region

3.1.1 Literature Search and Study Selection

In order to retrieve cancer costs from the MENA region to evaluate their methodological and reporting quality, their potential for transferability within the region and how can they be utilized to enhance evidence-based decisions and further research in the MENA, first, a systematic literature review was conducted to obtain all health economic evaluation studies from the region following the PRISMA guidelines.

The literature search was carried out on the Pubmed database till the date of 15th December 2019, using several filters including the English language, full-text journal articles, and combining the targeted countries in addition to the keywords related to the main outcomes, key methods and other general descriptions of health economic evaluation. Only studies from the following 17 MENA countries were selected: Algeria, Bahrain, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Palestine, Saudi Arabia (KSA), Syria, Tunisia, the United Arab Emirates (UAE) and Yemen. The detailed search strategy is included in Appendix (1). The entire screening process was done by two independent researchers in parallel.

After screening abstracts and titles, all English language full-text articles of original research on humans were considered eligible for review, if it concerned the local population of the respective MENA countries, and the reported costs were in monetary units between 1995-2019. Later on, eligible studies that were found in the reference lists from four systematic reviews from some of the countries in the region were also included. The full-text articles were examined by six researchers including me; the author, against the predefined eligibility criteria, and two supervising professors, where any discrepancies were resolved by consensus. My role at this stage involved preparing and managing a reference database to document all steps in researching PubMed, all the articles that have been allocated by the two researchers, and the screening criteria of the titles and abstracts of the selected publications

3.1.2 Data Extraction and Management

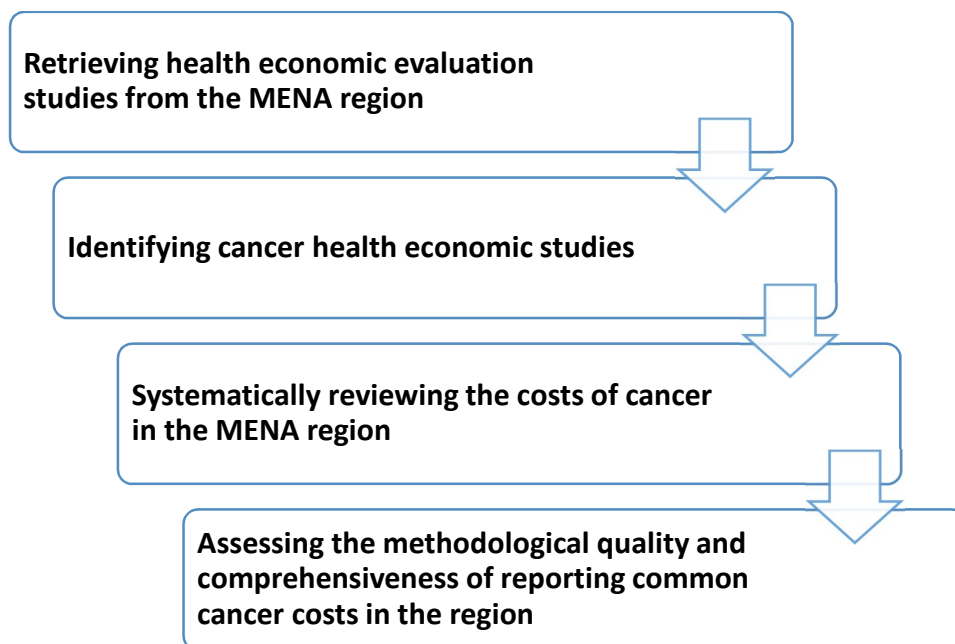
A Microsoft Excel spreadsheet was used for data extraction according to the predefined criteria. Data extraction was performed by the six independent researchers, including me the author in parallel. My role involved reading and checking 40 studies that were selected during the screening phase and systematically extracting healthcare cost units according to the defined criteria, peer-reviewing other 40 studies that were checked and its cost data were extracted by the other 5 student researchers, and organizing weekly calls and meetings with the leading supervisors where entries were cross-checked, and differences were resolved by common consent in a multi-phase process. First, the data was extracted from each one of the 206 publications, then the results were cross-checked during regular meetings under the supervision of the two senior researchers, and any arising differences were resolved by consensus.

The first author, publication year and country, and the cost items and cost country were extracted from each publication. The type of the economic analysis in each study was labeled as „*cost-utility analysis*” (CUA) if outcomes were QALYs or DALYs, „*cost-minimization analysis*” (CMA) if outcomes were documented to be equivalent and thus omitted from the comparison, „*cost-benefit analysis*” (CBA) if health outcomes were reported in monetary units, „*cost-effectiveness analysis*” (CEA) if outcomes were natural units, „*cost-comparison*” (CoC) when costs were compared without reporting outcomes, „*burden of disease*” (BoD) for descriptive studies including both costs and outcomes, „*cost-consequence analysis*” (CCA) if outcomes from multiple domains were reported in tabulated form, „*budget impact analysis*” (BIA) if the study concerned the financial consequences of adopting an intervention, „*efficacy study reporting costs*” (ErC) if costs were reported as secondary endpoints in clinical studies, „*benefit-incidence analysis*” (BeInA) if the analysis concerned the distribution of health care utilisation, and „*cost of disease*” (COI) when only costs were described. The perspective of the studies was also extracted or determined in case it was not reported, and categorized into the following categories: „*societal*”, „*patient*”, „*healthcare institution*”, „*health system*”, and „*other*”.

As for healthcare costs, the disease area including cancer and medical intervention as described by the author in addition to the year of cost collection, number of patients, currency, and the discount rates were extracted, followed by assigning the ICD-10 chapter- and diagnosis code to each cost item. Furthermore, the sector of costs was categorized as “*outpatient*” if cost referred to ambulatory care setting, “*inpatient*” if they concerned procedures or patients admitted to hospital,

and “*total*” in case costs covered both settings. When none of the predefined categories applied, they were categorized as “*not applicable*”

Cost categories were labeled as „*direct healthcare-*”, „*direct non-healthcare-*”, „*indirect-*” and „*total*” costs. The cost data sources were labeled as „*primary study*” if costs were collected directly during the respective study; „*assumption*” if costs were based on estimates or assumptions; „*model*” if costs were calculated via modeling; „*secondary local*” if costs were retrieved from local published sources for instance, government databases or publications and „*secondary foreign*” if the costs were adapted from foreign countries. The methods utilized by primary studies were labeled as „*healthcare institution*”, „*patient survey*”, and „*chart review*” in case of data originated from institutional accounting systems, „*insurance database*”, „*supplier pricelist*”, „*government database*”, „*expert/healthcare professional*” in case of third party expert advice and „*author*” if the estimates were performed by the study author. Finally, primary surveys were classified as „*prospective*”, „*retrospective*”, or „*cross-sectional*”. The predefined extraction spreadsheet was piloted at the first stage on a limited number of articles and refined at later stages.



Graph (5): Research scheme

3.1.3 Cancer Health Economic Evaluation and Costs

Following the general extraction of data and refining of the cost database, all studies that reported cancer costs and were categorized in disease chapter II Neoplasms were systematically reviewed

again and analyzed separately, to evaluate the health economic evaluation of cancer in the MENA region based on specific criteria such as stating study perspective, describing the medical intervention, time horizon, discounting of costs and outcomes and other descriptive elements.

The final step was finding a common cancer cost among these studies in order to perform a comparative analysis that assesses the quality of cancer costs reporting in the region, explore the key parameters that drive differences of the same cost among these countries, and checking whether this common cost is transferable among different jurisdictions within the region.

3.2 Assessment of Cancer Costs Reporting Quality

3.2.1 Quality Assessment: CHEERS Scoring

The quality and the risk of bias of five cancer health economic evaluations that covered cervical cancer and reported a common cancer cost; the annual cost of cervical cancer management, were assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. The CHEERS guideline is a 24 items checklist of guiding principles for documenting the results of health economic studies, through instructing the researchers on how to report transparent information and data in their studies, leading to better quality health economic evaluations. (Husereau et al., 2013)

The five publications were checked if they complied with certain items of the CHEERS guideline by examining if it's stated that the study followed the checklist, then investigating the publication thoroughly to inspect whether the study conformed with the chosen items from the guideline. The items that were specific to certain health economic evaluation studies such as cost-effectiveness studies, were not included in the final score. By going through the study details and checking whether it clearly stated that it complied with the CHEERS item such as reporting directly the discounting rate used or the perspective of the study or implying that, the study was given a score of 1, If not, or if there was no sufficient information to determine the answer, it was given a score of 0. In case the study complied with the proposed items partially, it was given a score of 0.5. Then, the total score of all items for each study has been summed up to give a score out of 18, to be used in further analysis. Table (3) shows CHEERS items that were included for the assessment.

CHEERS Section / Item	Item No	Recommendation
Title and abstract		
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods, results and conclusions.
Introduction		
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.
Methods		
Target population	4	Describe characteristics of the base-case population and subgroups analyzed including why they were chosen.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.
study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.
discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.
Estimating resources & costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, & conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
Results		
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate.
Characterising uncertainty	21a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).
	21b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.
Discussion		
Study findings	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge
Other		
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.

Table (3): CHEERS checklist items that have been included in the quality assessment of the five cancer health economic evaluation studies. (Source: Husereau, D., Drummond, M., Petrou, S., Carswell, C., Moher, D., & Greenberg, D. et al. (2013). Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMC Medicine*, 11(1). doi: 10.1186/1741-7015-11-80)

3.2.2 Common Cancer Costs

The following step as planned was finding common costs among the different countries to understand the heterogeneity and transferability of cancer costs between these MENA countries. Then a regression analysis was performed in order to answer this question, and understand how the quality of the health economic studies and other costing parameters would contribute to the variation of these costs, and how likely would these costs be transferrable among MENA jurisdictions. Therefore, 5 publications that were health economic evaluation of cervical cancer costs in the region and reported the annual management costs of cervical cancer per woman in the region were identified and used for further analysis. The annual management costs of cervical cancer per woman were used as a dependent variable in the regression analysis. Other common variables across the 5 studies were also searched for and tested whether they were predictors for explaining the heterogeneity among the common costs or not.

The cervical cancer cost that was the most commonly reported and consistent across the 5 studies, was the annual management cost of an unvaccinated woman with invasive cervical cancer, which was reported using local data sources and estimates. These costs were refined and checked carefully for which services and treatment they specifically included, in order to bring them into a common ground when conducting the comparison analysis. Where studies reported different annual management costs of cervical cancer according to the stage of the disease, the average of these costs was estimated and used as the annual average cost of cervical cancer management per woman.

3.2.3 Adjustments of the Common Costs

In health economic evaluations, it's often necessary to use cost data that have been collected at different time points. It's important that these costs that have been collected or estimated in different time periods are adjusted to be expressed in a base or reference year, which helps in making these cost data comparable. Without this adjustment, it might be difficult to determine whether a cost change of the medical intervention over time is caused by the change in the real

value of the used resources or due to a change in the purchasing value of the currency used to estimate these resources. (Turner, Lauer, Tran, Teerawattananon & Jit, 2019)

Therefore, to eliminate the impact of price fluctuation in the cost analysis, and ensure the comparability among studies conducted in different MENA countries and years, the cost data; annual cervical cancer costs per woman from the five studies were adjusted to 2020 values using the consumer price index of each costing country.

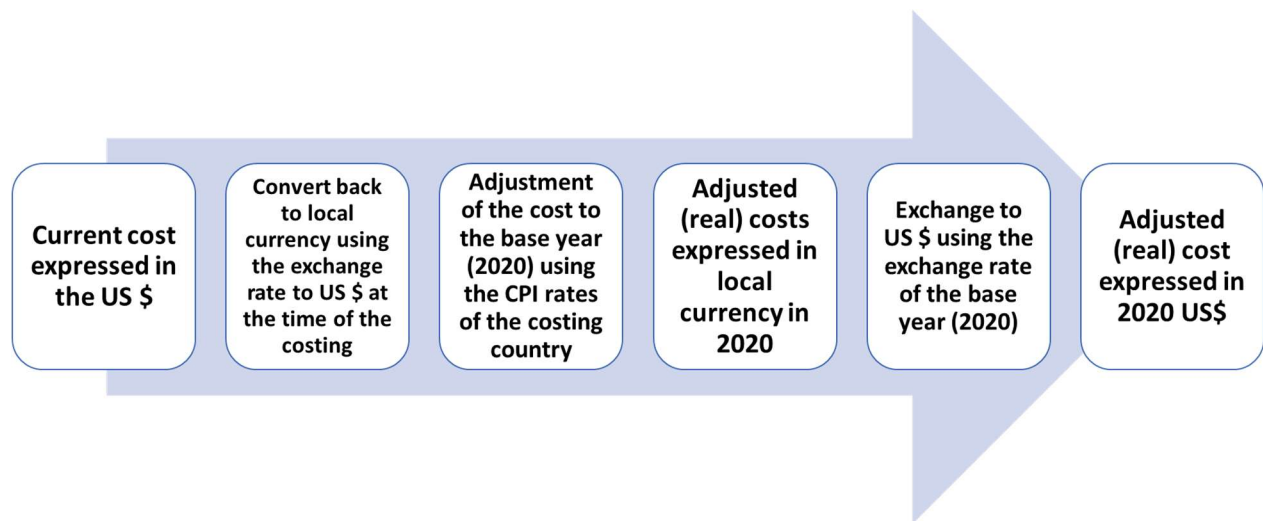
Additionally, in health economic studies that were conducted in low- and middle-income countries, the cost is often expressed in USD or international dollars, as found in four out of the five cervical cancer studies. However, It's vital to note that exchange rates change over time, therefore, before inflating the price to their current value, the costs should be converted back to their local currency using an exchange rate related to the time period when the cost data were collected, and then inflated and converted back to USD or international dollars using the exchange rate of the reference year. Otherwise, the costs might be notably over-adjusted (Turner, Lauer, Tran, Teerawattananon & Jit, 2019).

Considering these recommended adjustment methods, all the costs that were reported in USD in the studies were exchanged back to local currency as suggested by Turner's 2019 study. The steps of the adjustment are summarized in Graph (6). First, all the current costs that were expressed in the studies in USD were converted back to their local currency using the exchange rates of the costing year. Then, these costs were inflated to the value of the base year (2020) using the consumer price index CPI change rates of the costing country, producing adjusted costs that were expressed in the local currency. The final step was converting back these costs to USD using 2020 exchange rates. All the exchange rates were collected from both the World Bank and exchangerates.org.uk. The adjusted costs are referred to as real or constant costs, while the unadjusted costs are called nominal or current costs.

Afterward, the CPI data for each country were collected from both the World Bank and tardingeconomics.com. The change rate (increase or decrease) in the CPI has been calculated for each year starting from the costing year till reaching the base year (2020). Then the CPI change rates were multiplied with the cost to adjust it from the costing year value to the base year value.

This adjustment of costs will help in capturing the changes in the value of the currency over years, which is essential when using cost data of a treatment that was incurred over multiple years, or

when comparing cost data and results of health economic studies that have been conducted in different years. It's a vital step for research like this one when performing systematic literature reviews, making cost databases, and comparing economic evaluations from different countries. (Turner, Lauer, Tran, Teerawattananon & Jit, 2019).



Graph (6): Steps for adjusting the current costs to the real value in the base year (2020), as recommended by (Turner, Lauer, Tran, Teerawattananon & Jit, 2019).

3.2.4 Regression Analysis

A regression analysis was used to explore the association between cervical cancer costs and the commonly occurring potential predictors of costs. Sources of heterogeneity among the annual cervical cancer management costs per woman costs were explored by fitting some of the systematic differences in the studies characteristics such as costing year, whether the study followed a treatment guideline or no, the CHEERS quality scores of the study, the gross domestic product (GDP) per capita of the country, and the treatments that were included in the cost into both linear and multivariate regression analysis. Covariates were considered to be a source of variation if its regression coefficient was statistically significant ($p\text{-value} < 0.05$). The regression analyses were performed using IBM SPSS statistics 25 software.

Costing year was explored as an explanatory variable as some studies suggest that recent health economic evaluations might significantly report lower costs which might be due to changed clinical practices as well as methodological changes. (Williamson et al., 2017). While for the GDP per capita, and based on the evidence from the existing literature, there is a positive significant

relationship between national expenditure on healthcare and gross domestic product (GDP). (Nixon & Ulmann, 2006). For instance, in Kim 2013, Polynomial regressions suggested that GDP per capita explains approximately 80% of the variation in some of the WHO-CHOICE country-specific estimates such as hospital inpatient bed day costs and outpatient visit costs.

The quality of the study based on the CHEERS score was also explored as a possible predictor for the heterogeneity in the reported costs, to check whether a high-quality study might be linked to lower or higher costs. Finally, since there were some studies that reported following treatment guidelines and included some treatments such as brachytherapy and radiotherapy which were reportedly associated with higher costs, while other studies did not, the impact of these different clinical approaches were analyzed to check whether it has a relevance on the heterogeneity among these costs or not.

Potential predictors	Expected effect	Theoretical background
Costing year	Lower costs	Some studies suggest that recent health economic evaluations might significantly be associated with lower costs which might be due to changed clinical practices as well as methodological changes. (Williamson et al., 2017)
GDP per capita	Higher costs	Based on existing literature, there is a positive significant relationship between national expenditure on healthcare and gross domestic product (GDP). (Nixon & Ulmann, 2006).
CHEERS scores	to be determined	The quality assessment scores of the studies were explored as a predicting variable in heterogeneity, where studies that had higher costs are expected to have better and more transparent reporting quality, where the CHEERS checklist was considered as a quality assurance mechanism for economic evaluations (Husereau et al., 2013), to check whether there's a significant association between the quality of the study and heterogeneity of the costs.

Treatment protocol	to be determined	Clinical guidelines can be produced by governments or payers to help in controlling the raising healthcare costs which are derived from the increase in care demand and the aging population. Moreover, variations in care service among different providers, and delivery among providers, and jurisdictions are derived by the inappropriate care, either by overusing or underusing of healthcare services. This is why clinical guidelines and protocols are perceived by policymakers, payers, and healthcare providers as a tool used for quality improvement, consistent care, and efficient cost control. This is why it's used in this regression analysis to investigate whether it's associated significantly with lower or higher costs. (Woolf, Grol, Hutchinson, Eccles & Grimshaw, 1999)
Medical Interventions (Brachytherapy, radiotherapy, surgery)	Higher costs	Some of these studies included cancer treatments such as brachytherapy and radiotherapy which were reportedly associated with higher costs, while other studies did not. Therefore, the impact of these medical interventions was explored as a potential predictor of the heterogeneity in the costs, expecting higher costs to be associated with some of these interventions.

Table (4): Potential predictors of heterogeneity among the cancer costs and their expected impact.

4. Results and Analysis

4.1. Systematic Review of Health Economic Publications from the MENA Region

4.1.1 Search Results and Included Studies

This research presents the results of the systematic review of health economic evaluation studies including cancer health economic publications from the MENA region from 1995 until 2019. From 1646 relevant citations of full-text English articles retrieved from Pubmed search and 4 systematic reviews, 206 eligible studies were identified and included in the review, including 18 cancer health economic evaluation studies. Whereas 52 publications were eliminated for not meeting the eligibility criteria; 4 for not being an original study on human, one conference poster, 2 were not from the local MENA population, 15 for reporting costs older than 1995, 29 studies did not report costs at all and one duplicate study. PRISMA guidelines have been followed when reporting results as detailed in Figure (7). The full list of the 206 eligible studies can be found in appendix 2.

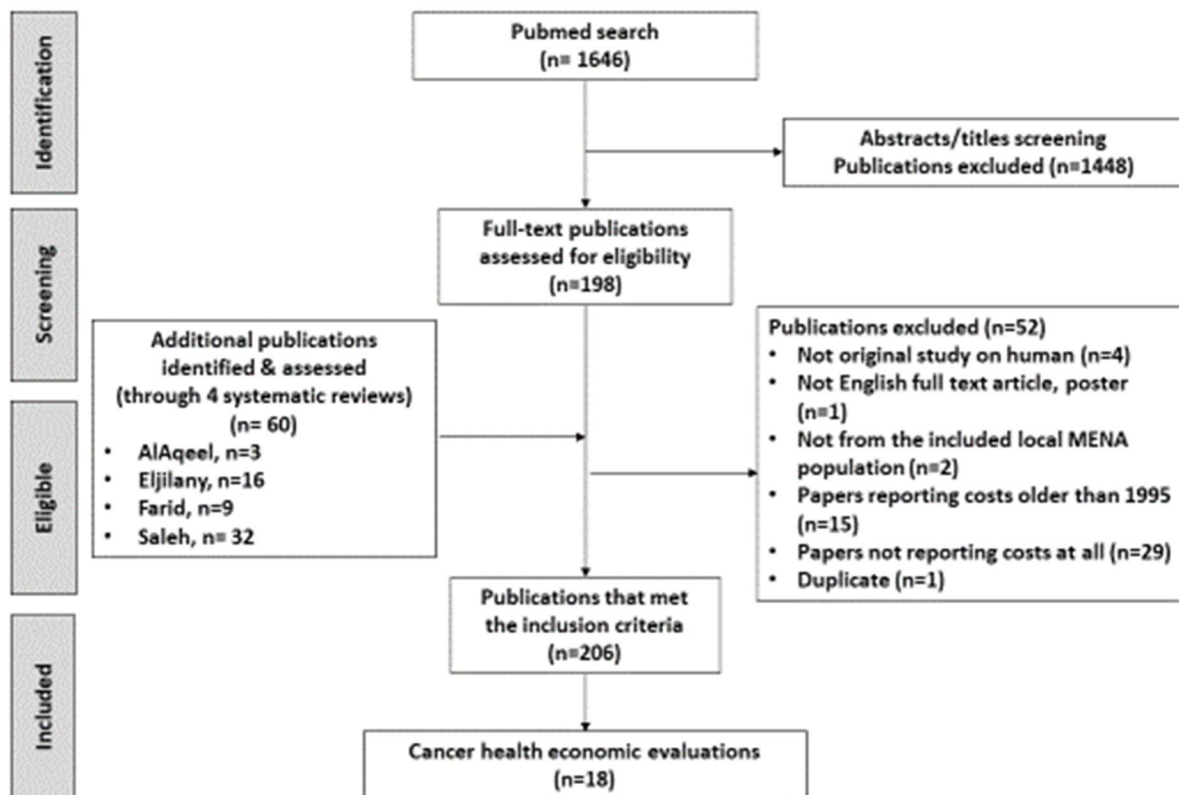
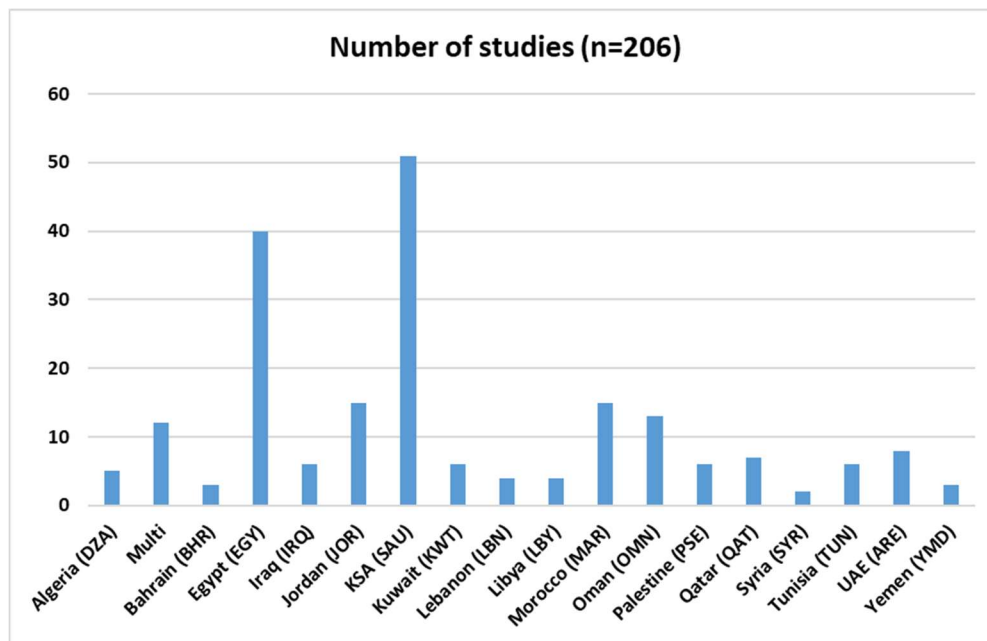


Figure (7): PRISMA flow diagram

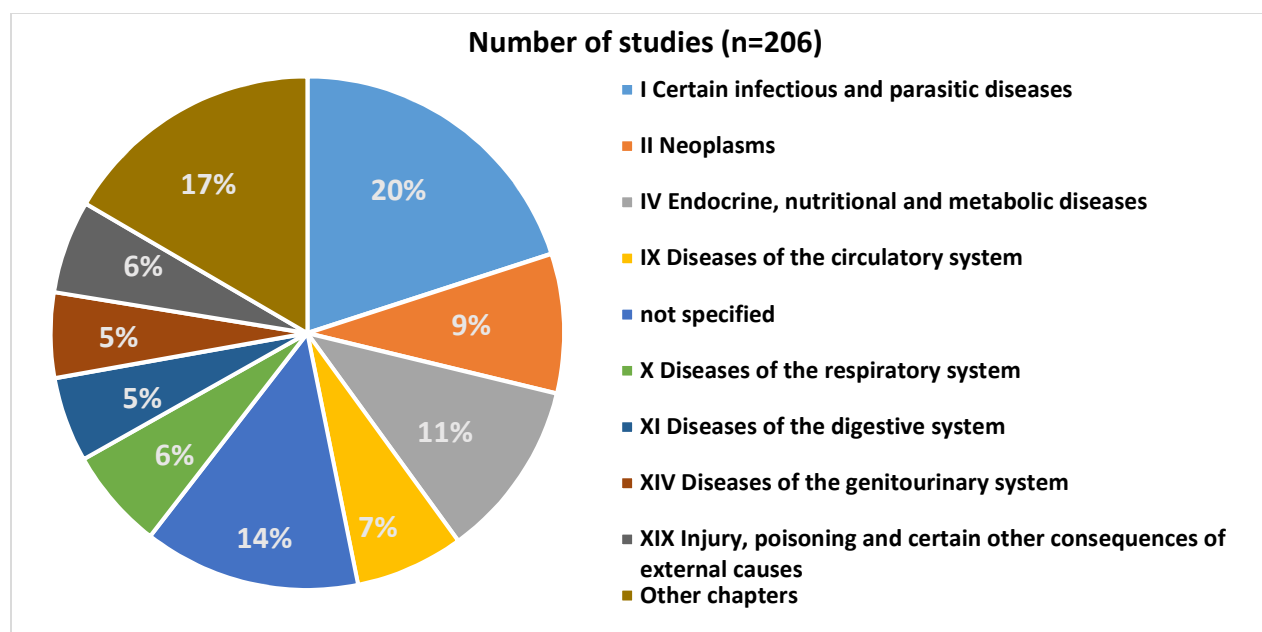
4.1.2 Characteristics of Studies

The majority of these studies were published in KSA (n=51), followed by Egypt (n=40), Jordan and Morocco (n=15 for each), and Oman (n=13). 158 studies out of the 206, were published from the year 2010. The 206 publications covered various disease areas and health interventions. The most common types of health economic evaluation found were cost of illness studies (n=42), cost-effectiveness analysis (n=40), cost-utility analysis (n=29), efficacy study reporting costs (n=29). Only 9 studies were cost-benefit analysis.

Studies from all the ICD-10 chapters were found, except for chapter XX; external causes of morbidity and mortality. The most common categories were chapter I, infectious diseases (41 studies), chapter IV, Endocrine, nutritional and metabolic diseases (24 studies), and chapter II, Neoplasms (18 studies). While 28 studies did not specify any particular disease area, and the patient population were only characterized by either the healthcare intervention used or the medical setting. While the most covered health interventions were vaccine programs (n=16), Diabetes Mellitus treatment programs (n=15), interventions for administration and staff management (n=12), and screening programs (n=12). Eleven publications did not define any specific healthcare treatments or programs for their costs.



Graph (8): Number of studies by publishing country (n= 206)



Graph (9): Distribution of studies by ICD-10 disease area (n=206). Other chapters includes all the other ICD chapters except of chapter XX.

The 206 eligible studies reported 3525 costs. The majority of these cost was reported by KSA (n=659), Egypt (n=566), Jordan (n=548), Palestine (n=264), Morocco (n=187), UAE (n=180), Qatar (n=157), and Oman (n=155). While the most frequent currency used in the retrieved costs was the US Dollar (n=1743), followed by Jordanian Dinar JOD (n=476), Saudi Riyal SAR (n=349), Egyptian Pound EGP (n=198), and Purchasing power parity PPP\$ (n=110).

More costs were found from the outpatient sector (n=1291), compared to the inpatient sector (n=1166), and total costs (n=808), while 260 costs were not assigned to any sector. Direct healthcare costs were the predominant cost category (n=2813) followed by total costs (n=406), direct non-healthcare costs (n=196) and indirect costs (n=137). The main source of these costs was primary study data (n=2440), whereas 300, 279, 209, and 207 costs were from models, assumption, secondary local and secondary foreign sources respectively. Finally, the majority of these costs were reported from the healthcare system perspective, whilst fewer costs were from the societal perspective.

Country	Number of costs by source						
	Model	Assumption	Estimates	Primary study	Secondary foreign	Secondary local	Study / RCT protocol costing

Algeria (DZA)	23	16	0	60	24	0	0
Bahrain (BHR)	0	0	0	16	3	0	0
Egypt (EGY)	132	68	5	266	11	56	28
Iraq (IRQ)	0	0	0	49	3	0	0
Jordan (JOR)	21	2	0	513	8	4	0
KSA (SAU)	70	10	0	477	33	43	26
Kuwait (KWT)	0	24	0	97	3	0	0
Lebanon (LBN)	6	4	0	15	3	1	0
Libya (LBY)	35	0	0	56	4	0	0
Morocco (MAR)	0	44	0	78	17	48	0
Oman (OMN)	0	28	0	114	9	4	0
Palestine (PSE)	7	9	0	247	0	1	0
Qatar (QAT)	0	4	0	147	3	3	0
Syria (SYR)	7	0	0	43	3	6	0
Tunisia (TUN)	7	5	23	77	6	5	0
UAE (ARE)	0	14	0	97	31	38	0
Yemen (YMD)	0	0	0	88	26	0	0
Multi countries	0	51	0	0	20	0	0
Grand Total	308	279	28	2440	207	209	54

Table (5): Costs by country and data source.

Country	Number of costs by cost category			
	Direct healthcare cost	Direct non healthcare cost	Indirect cost	Total cost
Algeria (DZA)	101	0	0	22
Bahrain (BHR)	15	0	1	3
Egypt (EGY)	491	1	10	64
Iraq (IRQ)	48	1	0	3
Jordan (JOR)	355	31	51	111
KSA (SAU)	585	8	32	34
Kuwait (KWT)	100	0	0	24
Lebanon (LBN)	27	0	1	1
Libya (LBY)	64	10	12	9
Morocco (MAR)	166	8	2	11
Oman (OMN)	140	4	7	4
Palestine (PSE)	190	18	1	55
Qatar (QAT)	155	0	1	1
Syria (SYR)	31	20	2	6
Tunisia (TUN)	98	15	5	5
UAE (ARE)	167	4	0	9

Yemen (YMD)	61	5	4	44
Multi countries	19	44	8	0
Grand Total	2813	169	137	406

Table (6): Costs by country and cost category.

4.1.3 Cancer Health Economic Evaluation

Out of the eligible 206 publications, 18 were cancer health economic evaluations which were published between the years 2007 and 2019. The studies covered 9 different cancer types including cervical cancer, hepatocellular carcinoma, brain cancer, colorectal cancer, prostate cancer, lung cancer, breast cancer, leukaemia, and multiple myeloma. It also included different medical interventions from vaccination and screening to chemotherapy. Most of these studies were published in Morocco (n=5), Egypt (n=4), KSA (n=3), Jordan (n=2), and Lebanon (n=2). One study, Kim 2013 reported costs from the Extended Middle East & North Africa (EMENA) which included Turkey, however, only costs from the local population studied were included in this research, leaving out the costs reported from Turkey. Six of these health economic evaluations were cost-effectiveness analysis, while 5 of them were cost of illness studies. The main characteristics of these cancer studies are summarized in Table (7) and Table (8).

Only 5 studies used discounting for the costs as recommended in health economic evaluations in order to reflect the opportunity cost of spending the money now rather than in the future. Additionally, 6 out of the 18 studies reported following treatment guidelines when valuing the resources and services used for managing the disease. Finally, as observed in the 206 studies, the majority of the cancer health economic evaluations were from the perspective of the healthcare system.

Publication ID	Publication country	Publication year	Disease	Intervention	Study Type	Number of Patients
Messoudi W	Morocco	2019	Cervical cancer	HPV vaccination	CEA	17 million *
Elsisi GH	Egypt	2019	Hepatocellular carcinoma	Sorafenib	CUA	NS
Elshahoubi A	Jordan	2019	Brain tumor	High-dose chemotherapy	CBA	7
Gamaoun R	Tunisia	2018	Cervical cancer	HPV vaccination	CMA	NS
Da'ar OB	KSA	2018	Cancer	NS	COI	10101

Arafa MA	KSA	2017	Prostate cancer	Screening	CEA	2898
Alefan Q	Jordan	2017	Colorectal cancer	colorectal cancer treatments	COI	97
Cheikh A	Morocco	2016	Cervical cancer	Cervical cancer treatments	COI	550
Eltabbakh M	Egypt	2015	Hepatocellular carcinoma	Screening	CEA	1286
Kim JJ	Multi	2013	Cervical cancer	HPV vaccination	CUA	NS
Berraho M	Morocco	2012	Cervical cancer	Cervical cancer treatments	COI	900
Tachfouti N	Morocco	2012	Lung cancer	NS	COI	3336
Alameddine M	KSA	2012	Bladder cancer	Cytology	BoD	563
Boutayeb S	Morocco	2010	Breast cancer	Trastuzumab & taxanes	CEA	5500
Denewer A	Egypt	2010	Breast cancer	Mammography	CEA	5900
El-Zawahry	Egypt	2007	Acute myeloid leukemia	Conventional chemotherapy (CCT)	BoD	82
Antar, A	Lebanon	2015	Multiple myeloma	G-CSF + hyperfractionated Cyclophosphamide	ErC	56
Salti, N	Lebanon	2014	Smoking	NS	COI	NS

Table (7): General characteristics of the 18 cancer health economic evaluation studies.

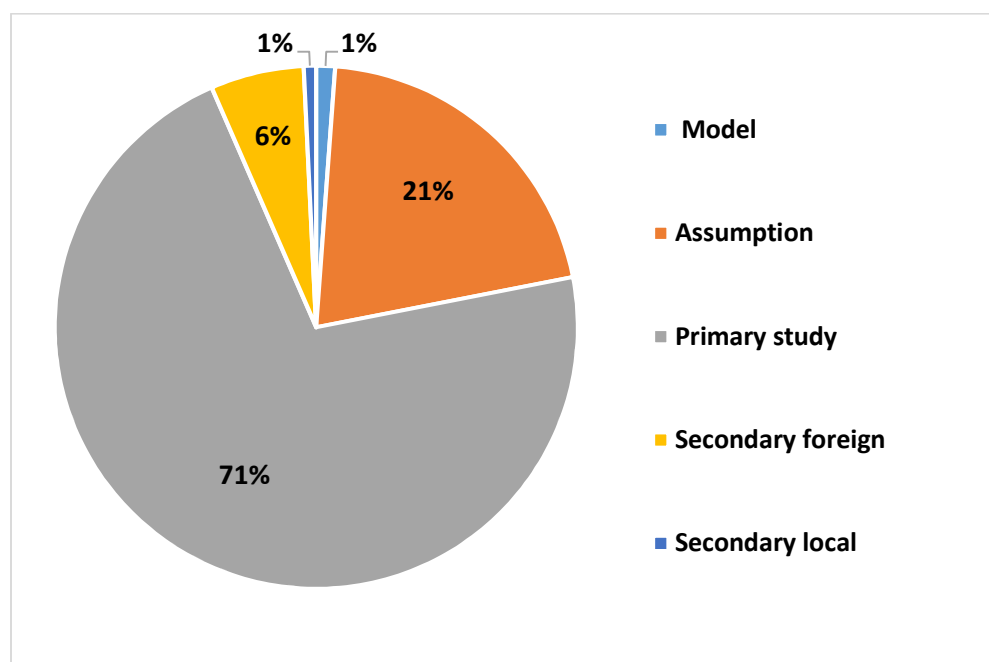
* Morocco Women population in 2015.

Publication ID	Data source	Treatment guidelines	Sensitivity analysis	Discount	Perspective
Messoudi W	Primary study	-	x	3%	Healthcare institution
Elsisi GH	Primary study	x	x	3.5%	Healthcare institution
Elshahoubi A	Primary study	-	-	-	Healthcare institution
Gamaoun R	Secondary local	-	-	3%	Health system
Da'ar OB	Model	x	x	3%	Health system
Arafa MA	Primary study	-	-	-	Health system
Alefan Q	Primary study	-	-	-	Healthcare institution
Cheikh A	Assumption	x	-	-	Health system
Eltabbakh M	Primary study	-	-	-	Health system
Kim JJ	Assumption	x	x	3%	Society
Berraho M	Primary study	x	-	-	Health system
Tachfouti N	Secondary foreign	x	-	-	Health system

Alameddine M	Primary study	-	-	-	Healthcare institution
Boutayeb S	Assumption	-	-	-	Health system
Denewer A	Primary study	-	-	-	Health system
El-Zawahry	Primary study	-	-	-	Healthcare institution
Antar, A	Primary study	-	-	-	Healthcare institution
Salti, N	Model	-	-	-	Health system

Table (8): Some features of the cancer health economic studies

260 cancer costs were found in these 18 studies that have been reported between the years 2002 and 2018 and were mostly direct healthcare costs (n=228). On the other hand, only a few total costs (n=29) and very few indirect and direct no-healthcare costs (n=2, n=1 respectively) were observed. Also, costs from the outpatient sector were the majority (n=144), when compared to the inpatient sector (n=60) and total costs (n=52). The sources of the data were mainly primary studies (n=186), assumptions (n=54), and secondary foreign data (n=15). Finally, various currencies were used when reporting cancer costs, including USD (n=128), Egyptian Pound EGP (n=53), Jordanian Dinar JOD (n=38), and Algerian Dinar DZD (n=20).



Graph (10): Distribution of cancer costs by data source.

4.1.4 Cervical Cancer Studies

When looking for a comparable common cancer cost in the studies to conduct analysis of the key parameters that derive heterogeneity among the same cancer cost in the region, five studies of

cervical cancer health economic evaluations reporting the cost of annual management of invasive cervical cancer per woman were found. Three of these cervical cancer studies were from Morocco, one from Tunisia, and one reported costs from multiple countries including Lebanon and Algeria. Together the five studies reported 86 healthcare costs, mostly from the outpatient sector (n=39) followed by total costs (n=33) and inpatient sector (n=14).

Three of these studies were cost-effectiveness analysis of cervical cancer interventions including screening and Human papillomavirus (HPV) vaccination, and two were cost of illness studies estimating the direct medical costs of cancer management in Morocco. Only three out of the five studies used discounting as the CHEERS guidelines recommend, while only two of them conducted sensitivity analysis. Table (9) shows the main features and differences of these studies.

All the studies were conducted from the perspective of the health system, except for Kim 2013 which reported costs from the societal perspective. It was also the only study that included indirect health costs such as women's time cost, and direct non-healthcare costs such as transportation costs.

Publication ID	Messoudi W	Gamaoun R	Cheikh A	Berraho M	Kim jj
Costing year	2018	2017	2013	2008	2005
Cost country	Morocco	Tunisia	Morocco	Morocco	Multi
Perspective	Health system	Health system	Health system	Health system	Societal perspective
Source of costs	Cost survey	Local & secondary sources	Local: NIO registry	The Moroccan National Agency for Health Insurance.	Primary local sources, publications, and estimations
Method	Markov model	PRIME Model + scientific literature	Micro-costing	Estimations	Mathmetical model
Medical Intervention	HPV vaccination & screening	HPV vaccination & screening	HPV vaccination & screening	Brachytherapy, radiotherapy, chemotherapy and surgeries	HPV vaccination & screening
Study type	CEA	CEA	COI	COI	CEA

Sensitivity analysis	One-way & two-way sensitivity analyses	NA	NA	NA	Sensitivity analyses and scenario analyses
Treatment guidelines	-	-	-	Clinical recommendations of AROME	Screening guidelines
Discounting	3% (on both costs & outcomes)	3%	NA	NA	3%

Table (9): Main characteristics of the cervical cancer studies

4.2 Assessment of Cancer Costs Reporting Quality

4.2.1 Quality Assessment: CHEERS Scores

The five cervical cancer publications were assessed for their methodological quality and for any risk of bias using 18 items of the CHEERS checklist for documenting the results of health economic studies. The studies generally proposed good CHEERS scores and showed compliance with guidelines when structuring the study and reporting the results. Both Messoudi 2018 and Kim 2013 had the highest scores of 18 points. While the Cheikh 2016 and Barreho 2012 the lowest scores of 12.5 points. The full results of assessments are presented in Table (10).

CHEERS criteria	Messoudi W	Gamaoun R	Cheikh A	Berraho M	Kim jj
Title	1	1	0.5	0.5	1
Abstract	1	1	1	1	1
Background and objectives	1	1	1	1	1
Target population	1	1	1	1	1
Setting and location	1	1	1	1	1
study perspective	1	0	0	0	1
Time horizon	1	1	1	1	1
Discount rate	1	1	0	0	1
Estimating resources & costs	1	1	1	1	1
Currency, conversion & price date	1	1	1	1	1
Assumptions	1	1	0	0	1
Analytical methods	1	1	0	1	1
Study parameters	1	1	1	1	1

Characterizing uncertainty	1	0	0	0	1
Characterizing heterogeneity	1	1	1	1	1
Study findings	1	1	1	1	1
Source of funding	1	1	1	1	1
Conflicts of interest	1	1	1	0	1
Total score	18	16	12.5	12.5	18

Table (10): Quality assessment among the cervical cancer studies using the CHEERS checklist.

4.2.2 Common Cancer Costs

The cervical cancer cost that was the most commonly reported and consistent across the 5 cervical cancer studies, was the annual management cost of an unvaccinated woman with invasive cervical cancer. Table (11) summarizes the costs that were included in the regression analysis from the 5 publications.

The cost that was included from the *Cheikh 2016* study was the average cervical cancer cost per woman from the total population for the year of cost. This cost includes treatments such as radiotherapy that accounts for 53% of the total cost, followed by brachytherapy (27%) and surgery (14%), and other services such as chemotherapy, radiological examinations, laboratory tests, and consultations which represented the remaining 6% of the cost.

In the *Gamaoun 2018* study, the cost which was reported as the incremental annual cost of medical care for an incident of cervical cancer was retrieved from a local Tunisian French study (Ben Gobrane et al. 2009). The local 2009 study has been examined to check the nature of the cost reported, which was the average direct medical cost for the management of cervical cancer cases during the first year after diagnosis and by the International Federation of Gynecology and Obstetrics (FIGO) staging system with an average of $3,180 \pm 1,391$ Tunisian Dinar.

The cost included the consumption of services such as surgery, radiotherapy, chemotherapy, and other items of various care consumption including the cost of consultations, hospitalizations, biological, radiological endoscopic explorations, and also associated palliative treatments. For the direct medical costs, no significant difference was found depending on the stage of the tumor, for the different treatment methods (surgery, radiotherapy, and chemotherapy), while the nature of patient care management varied according to the stage of the tumor. Among 11 patients diagnosed in stage I at the time of the discovery of the tumor, 8 were treated by surgery, mainly by

colpohysterectomy, enlarged or not; 10 patients received intravaginal brachytherapy. Nine received radiotherapy and 7 received chemotherapy. 12 Among the thirty-nine patients diagnosed with stage II, 31 underwent surgery, 10 of brachytherapy, 33 of radiotherapy, and 21 of chemotherapy. Of the 12 patients diagnosed at stage III, 6 were treated by surgery, 10 received brachytherapy, 12 received radiotherapy, and 8 received chemotherapy. Two patients were diagnosed at stage IV; they were treated with chemotherapy and radiotherapy. One patient had received chemotherapy and brachytherapy. (Ben Gobrane et al., 2009)

In *Barreho 2012*, the cost that was included was the average annual management costs of one invasive cervical cancer case by stage of diagnosis, which covers the diagnosis, treatment, and follow-up during the first year. Treatment included brachytherapy, radiotherapy, chemotherapy, and surgery. It was noted that depending on the type of treatment, both radiotherapy and brachytherapy contributed to the largest share of the cervical cancer treatment costs.

Similarly, in the *Messoudi 2019* study, the cost that was retrieved is the average treatment cost of the 4 stages of cervical cancer in addition to the cost of diagnostics (colposcopy and biopsy). The costs of Human papillomavirus (HPV) vaccine, the screening test (VIA), and CIN treatments (pre-cancerous lesions) were not included in the analysis. The study did not give any details regarding the exact treatments and services that were included in the calculation of the 4 stages of cancer treatment costs.

Finally, in *Kim 2013*, the average of the direct medical costs of the different cancer locations; that were classified based on invasive cervical cancer stages were included, which consist of the staging of cancer severity, hospitalization, stage-appropriate treatment, and follow-up visits, in addition to the costs of the cytology test and the cost for colposcopy/biopsy. In the direct medical costs, the study assumed that 10% of women with local cancer received a simple hysterectomy, while 90% received a total abdominal hysterectomy. For stage 1 cancer, it was assumed that 100% of women received surgery, while for stage 2, 20% received surgery and 80% underwent radiotherapy and chemotherapy. For stages 3 and 4 the assumption was that all women underwent radiotherapy and chemotherapy.

Once again, the HPV DNA test cost was not included, neither the CIN treatments. Moreover, estimates of women's time costs, traveling costs, and vaccination costs were not included as the

analysis focuses only on direct medical costs of cervical cancer management. Additionally, since only costs that were reported from local estimates or resource calculations were included in the regression analysis, the cervical cancer costs of Algeria were not included as they were estimated using Kenya as a base country for driving the costs.

Study	Country	Cervical cancer cost as described in the study	Cost	Currency	Cost components	Included treatments and services
Messoudi 2019	Morocco	Direct medical costs indexed at year 2018	1603.40	USD (\$)	The average of treatment costs of the 4 FIGO stages of cervical cancer + cost of diagnostics (colposcopy and biopsy).	Not specified
Gamaoun 2018	Tunisia	The incremental annual cost of medical care for an incident cervical cancer	3180.00	Tunisian Dinar (DT)	The average direct medical cost for the management of cervical cancer case during the first year after diagnosis and by FIGO stage	Surgery, radiotherapy, chemotherapy, consultations, hospitalizations, biological, radiological endoscopic explorations and associated palliative treatments.
Cheikh 2016	Morocco	Average annual cervical cancer costs	2599.00	USD (\$)	The average cervical cancer cost per woman from the total population for the year of costing.	Radiotherapy, brachytherapy, surgery, chemotherapy, radiological examinations, laboratory tests, and consultations.
Barreho 2012	Morocco	Estimation of Annual Management Cost of Cervical	5948.00	USD (\$)	The average of annual management cost of one cervical cancer case by FIGO stage of	Diagnosis, follow up services, and treatments including brachytherapy,

		Cancer for one patient			diagnosis during the first year of diagnosis.	radiotherapy, chemotherapy and surgery.
Kim 2013	Lebanon	Direct medical costs for screening, diagnosis, and treatment for cervical cancer	4714.68	International dollar (I\$)	The Average of treatment costs of Local, Regional and Distant Cancer + cost of cytology test + cost of diagnosis (colposcopy/biopsy test)	Staging of cancer severity, hospitalization, follow-up visits, cytology test, colposcopy /biopsy, hysterectomy, surgery, chemotherapy and radiotherapy.

Table (11): Cervical cancer costs that have been included in the regression analysis.

4.2.3 Adjustments of the Common Costs

The adjusted and inflated annual management costs of cervical cancer per woman based on the recommendation of Turner 2019 study are summarized in Table (12).

For the Messoudi 2019 study, prices were converted from USD as reported in the study in 2018, to Moroccan Dirham, then adjusted to 2020 using the CPI and converted back to USD using the average exchange rate from Moroccan Dirham to USD in 2020. In the Cheikh 2016 study, the costs were converted from USD as reported in the study to the local currency (Moroccan Dirham) value in 2013, then adjusted using the CPI from 2013 till 2020 and finally converted back to USD using the average 2020 exchange rate. Also, for Barreho 2012 the costs have been converted back from USD to Moroccan Dirham in 2008 then adjusted using the CPI to 2020 value then exchanged back to 2020 USD. In Gamaoun 2018, costs were already reported in Tunisian Dinar, so they were adjusted from 2009 to 2020 value then exchanged to USD. Finally, for Kim 2013 study, cervical cancer costs from Lebanon were converted from I\$ to Lebanese Lira then adjusted using the CPI to 2020 prices then converted back to USD.

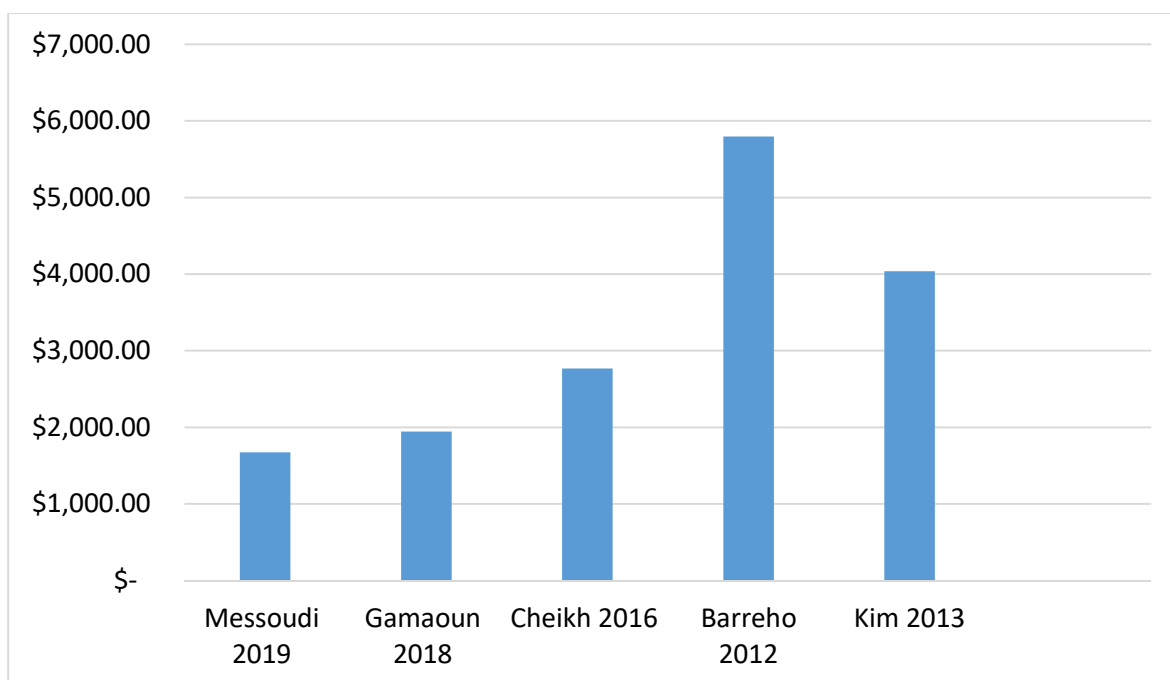
For some of the costing countries; Lebanon, the CPI data was not available before 2008 in any local or international sources, and since the costing year was 2005, the CPI value from 2005 to 2007 were estimated based on the CPI change rates for the following years, where the country generally was experiencing economic stability. However, it should be taken into consideration that

since 2019 Lebanon has ongoing liquidity crisis which is caused by various financial hardships in the government that led the Lebanese gross domestic product to fall to about 44 billion USD from about 55 billion USD the year before, and since October 2019, the consumer goods price has increased by 58%, which might affect the adjustment of the costs.

Among the adjusted (real) costs, the highest cost was 5,794.53\$ by *Barreho 2012*, and the lowest was 1,673.55\$ from the *Messoudi 2019* study. The mean of the adjusted cervical cancer management costs in 2020 was 3244.52\$, while the standard deviation from the mean value of the costs was 1696.57\$.

Study	Country	Current CC costs as reported in study	Current CC costs in local currency	Costing year	Adjusted cost (2020 prices) in local currency	Adjusted cost (2020 prices) in USD
Messoudi 2019	Morocco	\$ 1,603.40	MAD 15,049.51	2018	MAD 15,125.51	\$ 1,673.55
Gamaoun 2018	Tunisia	TND 3,180.00	TND 3,180.00	2009	TND 5,317.70	\$ 1,946.28
Cheikh 2016	Morocco	\$ 2,599.00	MAD 23,391.00	2013	MAD 26,630.13	\$ 2,769.07
Barreho 2012	Morocco	\$ 46,097.00	MAD 46,097.00	2008	MAD 5,794.53	\$ 5,794.53
Kim 2013	Lebanon	\$ 4,714.68	LBP 7,107,380.10	2005	LBP 22,013,610.12	\$ 4,039.19

Table (12): Adjustment of current costs to the base year value (2020)



Graph (11): Adjusted costs of annual cervical cancer management per woman (2020 value) in USD.

4.2.4 Regression Analysis

Results of the univariate and multivariate regression analysis is presented in Table (13). The GDP per capita of each costing country in 2020, the costing year and the quality assessment scores of the study (CHEERS scores) were not associated significantly with higher costs in both the univariate and the multivariate regression ($p > 0.05$). In the multivariate model, the three predictors explained 70.6% of the variance in the 2020 costs (R squared), and 17.4% of the variance when taking into consideration the number of these predictors in the regression model (Adjusted R squared). There was no evidence of Multicollinearity between the three variables.

Although it was observed that the costs were lower in more recent studies, with higher GDP, and higher CHEERS scores, there were no significant relation between these variables and the costs. In contrast, whether the study followed a treatment guideline for valuing the cancer management or not were significantly associated with higher costs ($p < 0.05$). Studies that reported following a treatment guidelines had on average 2787.22 USD higher cost.

Variable	Univariate regression		Multivariate regression	
	Marginal cost (USD 2020)	P-value	Marginal cost (USD 2020)	P-value
GDP 2020 per capita (USD)	-3.20	0.53	-3.74	0.63
Costing year	-215.11	0.25	-131.59	0.65
CHEERS Scores	-287.08	0.42	-375.12	0.50
Treatment protocol	2787.22	0.037		

Table (13): Univariate and multivariate analysis of adjusted cervical cancer costs using GDP, costing year, CHEERS scores and treatment protocols are predictors.

Finally, when the type of treatments that were included in the costs of cervical cancer management were explored as a predictable in a new multivariate regression model, non-showed any significant association with the cervical cancer costs, as seen in Table (14).

Variable	Univariate regression		Multivariate regression	
	Marginal cost (\$ 2020)	P-value	Marginal cost (\$ 2020)	P-value
Brachytherapy	646.90	0.73	-2092.91	0.61
Radiotherapy	1963.71	0.37	2365.64	0.57
Surgery	1963.71	0.37		
Colposcopy / Biopsy	-1728.79	0.328	-2335.52	0.53

Table (14): Univariate and multivariate analysis of adjusted cervical cancer costs using some of the treatments that were included in the cost as a predictor.

Based on these two regression models, neither of the variables that were explored as potential predictors including the GDP, time, reporting quality, and reported treatment components had a significant association with the variance among the same cost between the countries, therefore, non can be used when adjusting these costs. The heterogeneity of the same cancer cost reported among various studies from this region, is beyond the observation of this analysis, especially within the small sample size used in the analysis and the scarce cost data.

However, three of these cervical cancer costs were reported in the same country, Morocco, with an average cost of 3412.38 USD and a standard deviation (SD) of 2134.48. Despite the wide dispersion among the three costs in the same country, which can be an indicator of imprecision of locally available costs, it can be concluded if we would repeat the studies in Morocco, 68% of the cost results should fall between 1277.9 and 5549.86 USD, which is the mean cost $\pm$ SD (62.5% of the mean cost).

Therefore, the following hypothesis was developed and tested. It's recommended as a transferability method in the MENA region to calculate the average of as many costs even from past 5-10 years from as many countries as possible within the region while adding a certain measurement error, which is the percentage of SD compared to mean Moroccan costs. To test this hypothesis, the predicted costs were calculated using the average of the adjusted costs from different countries and studies and compared to the original costs to determine how accurate is our proposed hypothesis. For example, the Tunisian estimated cost was calculated using the average of the three Moroccan costs and the Lebanese cost. The predicted cost was 3569.09 USD. Then the difference between the predicted cost and the real cost that was retrieved from the Gamaoun 2018 study was calculated (1622.81 USD). The deviation from the original cost was 46.58%, which falls within the measurement error of the Moroccan cost that we used in our hypothesis. The same result was observed in the predicted Lebanese cost.

Table (15) summarizes the calculated predicted costs, using the mean calculation method compared against the actual costs in order to identify the prediction error and how close the transferred costs can get to the original costs when compared with the SD of the Moroccan costs. It also shows the third Moroccan cost prediction error (-93%) falls from the ratio of SD from the mean costs, indicating the difficulty of always predicting precise cost in Morocco due to the high variance of reported costs.

Study	Cost Country	Adjusted cost (2020 prices) in USD	Predicted cost	Diff	% of diff vs Mean	% of Moroccan SD vs Moroccan Mean
Messoudi 2019	Morocco 1	\$ 1,673.55	\$ 2,992.74	\$ 1,319.19	44.07%	62.5%
Gamaoun 2018	Tunisia	\$ 1,946.28	\$ 3,569.09	\$ 1,622.81	46.58%	62.5%
Cheikh 2016	Morocco 2	\$ 2,769.07	\$ 2,992.74	\$ 223.67	7.80%	62.5%
Barreho 2012	Morocco 3	\$ 5,794.53	\$ 2,992.74	\$ (2,801.80)	-93%	62.5%
Kim 2013	Lebanon	\$ 4,039.19	\$ 3,045.86	\$ (993.34)	- 32.61%	62.5%

Table (15): Evaluation of the results.

5. Discussion and Conclusion

The aim of this research is to give a broad insight into the health economic evaluation of cancer in the Middle East North Africa (MENA) region over the past 25 years. It also seeks to identify the possible gaps in reporting cancer costs that might hurdle the development of future health economic research of cancer in the region, particularly, in regard to scaling up the health benefits and patient's quality of life while optimizing the utilization of the available limited resources. To the best of our knowledge, this is the first research that systematically reviews the cancer health economic evaluation publications and assesses the quality of cancer costs reporting in the MENA region.

5.1 General Discussion

5.1.1 Systematic Review

This research reviewed and analyzed cancer costs published in cancer health economic studies as part in the countries from the MENA region between 1995 and 2019. 206 eligible health economic evaluation studies were identified including more than 3500 cost data. The studies were published in 17 countries from the MENA region, including studies that reported cost data from multiple countries, however, KSA, Egypt, Jordan, and Morocco were the top publishing countries. Most of these studies were cost of illness studies, cost-effectiveness analysis, and cost-utility analysis.

Disease from all the ICD-10 chapters was covered by the studies, except for chapter XX; external causes of morbidity and mortality. Health economic evaluation of infectious diseases, endocrine, nutritional and metabolic diseases, and neoplasms were the most common found studies. 158 studies out of the 206, were published from the year 2010 onward, indicating that the region in the last decade is witnessing increased attention to the importance of health economic evaluation in managing healthcare resources.

The 3525 costs were mostly reported using USD currency, as observed by Turner's 2019 study where it's typical in low and middle-income countries to report their costs in USD. Direct healthcare costs represented a significant number in the cost data when compared to non-direct healthcare costs and indirect costs. This suggests that despite the increasingly positive attention to health economic evaluation in the region, these studies are not inclusive to all aspects of healthcare costs such as productivity losses, time costs, and informal care, which might lead to

underestimation of the real value of the evaluated new medical intervention or the real burden of disease.

Moreover, the majority of these costs were reported from the health system perspective, whilst fewer costs were reported from the societal perspective, despite the recommendation of including the societal perspective that incorporates that all costs and health-effects regardless of who incur the costs and who obtain the benefits, in order to reflect the board analytical perspective for decision-maker when allocating resources across the entire population. (Sanders et al., 2016) (Drummond, Sculpher, Claxton, Stoddart & Torrance, 2015)

18 studies from the 206 eligible studies were cancer health economic evaluations, reporting the costs related to different types of cancer and different medical interventions. Nevertheless, it was observed that there was not enough health economic research on the public health priorities of cancer in the region, where only two studies evaluated breast cancer, one for liver cancer and one for lung cancer, despite that these cancer locations have the highest-burden in the region.

Moreover, there was a scarcity of studies from the societal perspective, where only one out of the eighteen cancer studies reported the results from the societal perspective. Also, very few indirect cancer healthcare costs were found. This exclusion of indirect medical costs can lead to bias in health economic evaluation, especially cost-effectiveness studies by underestimating the real cost of cancer and some cancer medical interventions in these countries. It might lead to an increased burden on cancer patients and caregivers as well.

Another element that lacked in many of these studies, was discounting. Only five studies used discounting on their future costs and outcomes as recommended in health economic evaluation in order to reflect the real local economic conditions. This might lead to the assumption that these cancer costs will not reflect precisely for decision-makers the real opportunity cost of spending their budget on cancer care now rather than in the future.

5.1.2 Assessment of Cancer Costs

Out of the 86 cancer costs that were identified, only 5 relevant common cancer costs could be found to be included in the regression analysis across the studies. The mean for these annual invasive cervical cancer management costs per woman, after the adjustment to the base year (2020) was 3244.52\$, with some heterogeneity between the studies. The same costing country; Morocco

reported both the highest cost (5,794.53 USD) and the lowest (1,673.55), indicating the heterogeneity in costs reporting even on a local level.

Appraising the five cervical cancer studies' quality, using some items of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, showed relatively good scores especially among the newly published studies, indicating that the importance of health economic evaluation is increasing in the region. Some studies which were cost-utility analysis did not fit with some of the CHEERS checklist items. Therefore, only items that could be applied to all health economic studies were used to appraise the quality.

In the regression analysis, the factors related to the country and healthcare system (GDP per capita), the study quality (CHEERS scores), and the costing year were not statistically significant when associated with the cervical cancer costs. The same for the role of some of the treatments and medical interventions that were included in the cost (brachytherapy, surgery, radiotherapy, and colposcopy), which showed no evident connection with the heterogeneity in the reported costs. On the other hand, studies that used treatment protocols when valuing the healthcare services provided for managing cervical cancer were significantly associated with higher cervical cancer costs. However, there was not enough data to help in understanding this significance and interpret the real impact of utilizing treatment guidelines on reporting costs.

These results lead to the conclusion that the region has a huge instability when it comes to the health financing systems. There's a certain variability in cancer costs among MENA countries and even within the same country regardless of the country's economic situation, the costing and reporting methodology when were these costs reported, or what were the treatments used. This heterogeneity is beyond what could be explained from these cancer health economic studies.

However, it also suggests that these costs which have been retrieved from the past can still be used nowadays by simply knowing the GDP of the country in the costing year. For example, the costs that were reported from Lebanon 10 years ago, and regardless of the financial crisis, can still be used in 2020 using a reasonable comparison. Moreover, for estimating cancer costs for another country in the region, the average of the same cancer cost from different MENA countries can be used with sensitivity analysis and a specific standard error for these costs. This approach in cost transferability is recommended over, for example, what Kim 2013 used for estimating Algerian cancer costs, which has been derived only from one country, Kenya. This recommended strategy

of using the average cost from a greater number of countries, while using a reasonable relationship between per capita Gross Domestic Product and the cost year, is more likely to produce more accurate and transparent cancer costs estimation.

Although this method might not be the most accurate method for transferring cancer costs within the regions, it led to the estimation of costs that are not highly divergent from the original real costs found in these cancer studies, despite the very limited number of cost data available for analysis. If this hypothesis was very imprecise, then the predicted costs would have been notably way higher or lower than the actual costs.

5.2 Strengths and Limitations

To our knowledge, this is the first research to undertake a systematic review and transferability analysis of cancer health economic studies and costs in the MENA region. A large number of health economic evaluation studies including 18 cancer studies from 17 different countries have been identified, reporting more than 3500 costs over the course of 25 years. The literature search has been done by two independent researchers, followed by analyzing the selected studies and costs by another six independent researchers including myself; the author, where any discrepancies were resolved by consensus.

The results found in this research regarding cancer costing in the region can guide researchers on measures, factors, and strategies to include in future health economic evaluation of cancer in the region in order to generate more accurate and transparent cost data, by giving an insight of the gaps in the current health economic practices and how it should be improved in future research. It also provides practical recommendation of how these cancer cost data can be utilized and transferred across jurisdictions within the region while generating reliable estimates that helps in saving time and resources.

However, there were several limitations in this research within the scope of the selected reviewed studies and the research itself. First, despite the large number of costs that were extracted, the number of common cancer costs that were found in the 18 studies was very low, which means that only a few cancer costs were robustly analyzed using regression analysis techniques. Additional cost data would have ensured more well-grounded results of the regression analysis, and adjusting the costs for a wider range of variables.

Second, even the costs that were included were somehow variable with respect to the study costing methods and reporting, and the data sources. For example, one study reported the summary cost without providing the breakdown of the direct medical costs that were included, suggesting ambiguity regarding the source and quality of these costs. Also, two of these studies did not include a basic statement about discounting the costs creating further doubt in their economic methods. In contrast, some of these studies were of high quality as they described in detail their costing methods and some other recommended health economic evaluation criteria such as discounting. This demonstrates the importance of detailed reporting of the methods and resources that have been used in cancer cost calculations. Inconsistency in methods among these studies and the lack of transparency in some of them might be one of the reasons behind the unexplained variation in cancer cost estimates.

Moreover, when adjusting the costs to their real value in 2020, different sources have been used to collect data about the GDP per capita and the consumer price index (CPI) for the reporting countries, and for Lebanon, the CPI values before 2008 have been estimated due to the lack of sufficient data. Consequently, this might affect the accuracy of the cost analysis results.

Finally, and as stressed previously, indirect costs of cervical cancer such as productivity loss and informal care were not included in the analysis, due to the scarcity of these costs in the region. Which in its turn affects the inclusiveness of this research results in giving a broad recommendation when it comes to the transferability of cancer costs. Estimates of indirect cancer costs that covers all individuals and all aspects including patients and caregiver lost productivity, time costs and mortality costs are highly significant, and have to be included in future research along with the direct medical costs in order to reflect a clear vision of the economic burden of cancer on the MENA region.

5.3 Conclusion

The MENA region is witnessing an epidemiological shift toward non-communicable diseases as the rest of the world, and cancer is one of the main leading causes of NCDs-related deaths in the region. It's expected that by 2030, MENA countries will have the highest cancer burden in the world. Additionally, the costs of cancer care have increased drastically over the past years, with more out-of-pocket spending and highly expensive new targeted interventions such as therapeutic

agents which pose a high financial burden to the patients and their families, and the health budget of these low and middle-income countries.

In order to provide policymakers and stakeholders of the region with more reliable and comparable cancer cost data, that maximizes the health benefits of the population while ensuring the optimal gain from the limited resources, it's vital at this stage to enforce the role of health economic evaluation and standardize the economic methods when estimating healthcare resources in cancer management. Systematizing the treatment guidelines and definitions and following health economic evaluation guidelines such as the CHEERS checklist, including indirect cancer costs and the perspective of society when conducting health economic analysis will also help in reducing the heterogeneity in costs estimation, and eliminating bias when reporting these costs.

Finally, until high-quality cost data is made available in the MENA region when transferring costs among jurisdictions of the region, it's recommended to take the average of the same cancer cost that was already reported in different countries within the MENA, and estimating the new cost for the jurisdiction through using sensitivity analysis and a certain standard error, in order to provide more accurate cost estimates, rather than relying only on the estimates of one country as it was done by previous studies.

Heterogeneity among studies is unavoidable. However, guidelines and checklists, transparent methods, and standardized cost reporting can help in implementing sufficient, accurate, and transferable cancer health economic evaluation in the MENA region. Finally, these methods and recommendations should be focused first and foremost on the cancer public health priority of the region.

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Appendixes

Appendix (1): PubMed search strategy

Health economics	(("outcomes"[Title/Abstract] AND "costs"[Title/Abstract]) OR ("outcomes"[Title/Abstract] AND "cost"[Title/Abstract]) OR ("outcome"[Title/Abstract] AND "costs"[Title/Abstract]) OR ("outcome"[Title/Abstract] AND "cost"[Title/Abstract]) OR ("benefits"[Title/Abstract] AND "costs"[Title/Abstract]) OR ("benefits"[Title/Abstract] AND "cost"[Title/Abstract]) OR ("benefit"[Title/Abstract] AND "costs"[Title/Abstract]) OR ("benefit"[Title/Abstract] AND "cost"[Title/Abstract]) OR "cost saving"[Title/Abstract] OR "cost savings"[Title/Abstract] OR "cost analysis"[Title/Abstract] OR "cost benefit analysis"[Title/Abstract] OR "cost analysis"[Title/Abstract] OR "economic evaluation"[Title/Abstract] OR "economic appraisal"[Title/Abstract] OR "cost effectiveness"[Title/Abstract] OR "cost utility"[Title/Abstract] OR "cost consequence"[Title/Abstract] OR "cost minimization"[Title/Abstract] OR "budget impact"[Title/Abstract] OR "decision model"[Title/Abstract] OR "HTA"[Title/Abstract] OR "health technology assessment"[Title/Abstract] OR "COI"[Title/Abstract] OR "cost of illness"[Title/Abstract] OR "cost of disease"[Title/Abstract] OR "CEA"[Title/Abstract] OR "CBA"[Title/Abstract] OR "CMA"[Title/Abstract] OR "CUA"[Title/Abstract] OR "DALY"[Title/Abstract] OR "QALY"[Title/Abstract] OR "quality adjusted life years"[Title/Abstract] OR "quality adjusted life year"[Title/Abstract] OR "disability-adjusted life years"[Title/Abstract] OR "disability-adjusted life year"[Title/Abstract] OR "ICER"[Title/Abstract] OR "cost effectiveness ratio"[Title/Abstract] OR "ACER"[Title/Abstract] OR "Markov model"[Title/Abstract] OR "quantitative evaluation"[Title/Abstract] OR "decision tree"[Title/Abstract] OR "health economic"[Title/Abstract] OR "discrete event simulation"[Title/Abstract] OR "program evaluation"[Title/Abstract] OR "decision making"[Title/Abstract] OR "expenditure"[Title/Abstract] OR "economic model"[Title/Abstract] OR "friction cost"[Title/Abstract] OR "contingent valuation"[Title/Abstract] OR "medical cost"[Title/Abstract] OR "medical costs"[Title/Abstract] OR "disease related cost"[Title/Abstract] OR "disease related costs"[Title/Abstract] OR "direct cost"[Title/Abstract] OR "direct costs"[Title/Abstract] OR "indirect cost"[Title/Abstract] OR "indirect costs"[Title/Abstract] OR "cost comparison"[Title/Abstract] OR "resource utilization"[Title/Abstract] OR "economic burden"[Title/Abstract] OR "pharmacoeconomic"[Title/Abstract] OR "pharmacy economic"[Title/Abstract] OR "cost effective"[Title/Abstract])
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Supplementary Table 1. continued

Countries	egypt11[Title/Abstract] OR egypt24[Title/Abstract] OR egypt35[Title/Abstract] OR egypt7[Title/Abstract] OR egypta5[Title/Abstract] OR egyptae[Title/Abstract] OR egyptain[Title/Abstract] OR egyptalum[Title/Abstract] OR egypte[Title/Abstract] OR egyptensis[Title/Abstract] OR egypti[Title/Abstract] OR egyptia[Title/Abstract] OR egyptiaca[Title/Abstract] OR egyptiacae[Title/Abstract] OR egyptiacum[Title/Abstract] OR egyptiacus[Title/Abstract] OR egyptial[Title/Abstract] OR egyptiam[Title/Abstract] OR egyptian[Title/Abstract] OR egyptian'[Title/Abstract] OR egyptian's[Title/Abstract] OR egyptiandecent[Title/Abstract] OR egyptianellosis[Title/Abstract] OR egyptianization[Title/Abstract] OR egyptianization'[Title/Abstract] OR egyptianizing[Title/Abstract] OR egyptianpatients[Title/Abstract] OR egyptians[Title/Abstract] OR egyptians'[Title/Abstract] OR egyptianum[Title/Abstract] OR egyptica[Title/Abstract] OR egypticum[Title/Abstract] OR egyptiens[Title/Abstract] OR egyptinan[Title/Abstract] OR egyptiologists[Title/Abstract] OR egyption[Title/Abstract] OR egyptiorum[Title/Abstract] OR egyptius[Title/Abstract] OR egypto[Title/Abstract] OR egyptological[Title/Abstract] OR egyptologist[Title/Abstract] OR egyptologists[Title/Abstract] OR egyptology[Title/Abstract] OR egyptomania[Title/Abstract] OR egyptox[Title/Abstract] OR egyptys[Title/Abstract] OR (iraq[Title/Abstract] OR iraq'[Title/Abstract] OR iraq's[Title/Abstract] OR iraqbodycount[Title/Abstract] OR iraqensis[Title/Abstract] OR iraqi[Title/Abstract] OR iraqi's[Title/Abstract] OR iraqian[Title/Abstract] OR iraqibacter[Title/Abstract] OR iraqibacter'[Title/Abstract] OR iraqiensis[Title/Abstract] OR iraqis[Title/Abstract] OR iraqis'[Title/Abstract] OR iraqne[Title/Abstract] OR iraqnophobia[Title/Abstract] OR iraqp[Title/Abstract] OR iraqp1[Title/Abstract] OR iraquara[Title/Abstract] OR iraque[Title/Abstract] OR iraquensis[Title/Abstract] OR iraqui[Title/Abstract] OR iraquis[Title/Abstract] OR iraqw[Title/Abstract] OR iraqwi[Title/Abstract]) OR Jordan[Title/Abstract] OR Kuwait[Title/Abstract] OR Leban[Title/Abstract] OR Libya[Title/Abstract] OR (moroccan[Title/Abstract] OR moroccan'[Title/Abstract] OR moroccan's[Title/Abstract] OR moroccanisolates[Title/Abstract] OR moroccans[Title/Abstract] OR moroccans'[Title/Abstract] OR moroccanshad[Title/Abstract] OR moroccanus[Title/Abstract] OR moroccari[Title/Abstract] OR morocco[Title/Abstract] OR moroccean[Title/Abstract] OR moroccensis[Title/Abstract] OR morocciensis[Title/Abstract] OR morocco[Title/Abstract] OR morocco'[Title/Abstract] OR morocco's[Title/Abstract] OR moroccoan[Title/Abstract] OR moroccoensis[Title/Abstract] OR morocolide[Title/Abstract] OR moroccon[Title/Abstract]) OR Oman[Title/Abstract] OR Qatar[Title/Abstract] OR Saudi[Title/Abstract] OR Syria[Title/Abstract] OR (tunis[Title/Abstract] OR tunis'military[Title/Abstract] OR tunis's[Title/Abstract] OR tunisa[Title/Abstract] OR tunisan[Title/Abstract] OR tunisean[Title/Abstract] OR tunisee[Title/Abstract] OR tunisee'[Title/Abstract] OR tuniseus[Title/Abstract] OR tunisi[Title/Abstract] OR tunisia[Title/Abstract] OR tunisia'[Title/Abstract] OR tunisia's[Title/Abstract] OR tunisialbus[Title/Abstract] OR tunisian[Title/Abstract] OR tunisian'[Title/Abstract] OR tunisian's[Title/Abstract] OR tunisian1995[Title/Abstract] OR tunisiana[Title/Abstract] OR tunisians[Title/Abstract] OR tunisians'[Title/Abstract] OR tunisicus[Title/Abstract] OR tunisie[Title/Abstract] OR tunisien[Title/Abstract] OR tunisienne[Title/Abstract] OR tunisiens[Title/Abstract] OR tunisiense[Title/Abstract] OR tunisiensis[Title/Abstract] OR tunisification[Title/Abstract] OR tunisina[Title/Abstract] OR tunision[Title/Abstract] OR tunisite[Title/Abstract] OR tunisostertagia[Title/Abstract] OR tunispinosides[Title/Abstract] OR tunisvirus[Title/Abstract]) OR UAE[Title/Abstract] OR "United Arab Emirates"[Title/Abstract] OR Dubai[Title/Abstract] OR "Abu Dhabi"[Title/Abstract] OR Yemen[Title/Abstract] OR Palestine[Title/Abstract])
	AND
Filters	("loattrfull text"[sb] AND English[language])

Citation

Appendix (2): The full list of the selected 206 eligible studies

Author, Year	Cost year	Country	Disease	Intervention	Number of cost Items	Number of patients
Salman RA, 2019 [1]	2015	Bahrain (BHR)	Diabetes mellitus	Type 2 diabetes treatment	9	628
Al-Senani F, 2019 [2]	2019	KSA (SAU)	Stroke	Acute & rehabilitation service staffing	11	Not specified
Nasef R, 2019 [3]	2017	UAE (ARE)	Bacteremia	PCR blood screening in antibiotic stewardship program	4	477
Almalki Z, 2019 [4]	2018	KSA (SAU)	Hypertensive heart disease	Intensive blood pressure treatment	9	44989
Alefan Q, 2019 [5]	2016	Jordan (JOR)	Not specified	Medication management review (MMR) and the home medication management review (HMMR)	36	845
Labib ME, 2019 [6]	2018	Egypt (EGY)	Dental caries	Selective versus stepwise removal of deep carious lesions	8	115
Alomar MJ, 2019 [7]	Not specified	KSA (SAU)	Diabetes mellitus	Treatment of diabetes type2	6	101
AlBaty A, 2019 [8]	2018	KSA (SAU)	Oral conditions	Determinants of catastrophic expenditure (payment methods)	40	500
Hersi AS, 2019 [9]	2013	KSA (SAU)	Atrial fibrillation	Apixaban for stroke prevention	34	1000
Al-Qudah RA, 2019 [10]	2017	Jordan (JOR)	Not specified	Clinical pharmacist intervention to prevent drug adverse events	6	97
Messoudi W, 2019 [11]	2018	Morocco (MAR)	Cervical cancer	HPV vaccination (cervical cancer prevention)	10	1700000
Al-Senani F, 2019 [12]	2018	KSA (SAU)	Stroke	Care program development (reperfusion centres)	4	3341366

Alowayesh MS, 2019 [13]	2015	Kuwait (KWT)	Multiple sclerosis	MS management	43	1344
Kaci Z, 2019 [14]	2015	Algeria (DZA)	Agranulocytosis	Diagnosis driven Therapy of invasive fungal infections	30	592
Kadem SG, 2019 [15]	2017	Iraq (IRQ)	Thyroid disease	Bipolar radiofrequency ablation device vs ultrasonic scalpel	4	60
Knott RJ, 2019 [16]	2014	KSA (SAU)	Injury	Erythropoietin	10	606
Abushanab D, 2019 [17]	2017	Qatar (QAT)	Respiratory distress	Morphine vs fentanyl	75	126
Mostafa A, 2019 [18]	2017	Egypt (EGY)	Not specified	Safety needles to prevent HBV, HCV and HIV	22	18378
Pugh SJ, 2019 [19]	2016	Algeria (DZA), Tunisia (TUN)	Pneumococcus	Pneumococcus vaccination	32	Not specified
Mourad S, 2018 [20]	2013	Egypt (EGY)	Stress urinary incontinence	Autologous versus synthetic slings	2	62
Abdulhamid AK, 2018 [21]	2017	Iraq (IRQ)	Thyroid disease	Abdominal drainage	2	227
Elsisi GH, 2019 [22]	2017	Egypt (EGY)	Hepatocellular carcinoma	Sorafenib	12	Not specified
Vallasciani S, 2019 [23]	2017	KSA (SAU)	Urological conditions	Telehealth assessment	11	105
El Hadi H, 2019 [24]	2016	Morocco (MAR)	Hepatitis C	A one-step reverse transcription quantitative PCR (RT-qPCR) assay	2	Not specified
Elshahoubi A, 2019 [25]	2015	Jordan (JOR)	Brain tumor	High-dose chemotherapy protocols	10	7
Bouame M, 2018 [26]	2017	Algeria (DZA)	Atrial fibrillation	estimate the economic burden of NVAf in Algeria	30	187686
El-Ghitany EM, 2019 [27]	2015	Egypt (EGY)	Hepatitis C	EGCRISK application vs mass screening	13	60464323
Cara AKS, 2018 [28]	2013	KSA (SAU)	Pneumonia	Low versus high dose colistin	10	96

Morris TF, 2018 [29]	2017	KSA (SAU)	Not specified	Demand management of laboratory services	12	Not specified
Gamaoun R, 2018 [30]	2017	Tunisia (TUN)	Cervical cancer	HPV vaccination (cervical cancer prevention)	9	Not specified
Abdelrazik AM, 2018 [31]	2017	Egypt (EGY)	Hepatitis C	Hepatitis C Virus (HCV) core antigen	2	1850
Montaut S, 2018 [32]	2016	Algeria (DZA)	Movement disorders	Assessment of a Targeted Gene Panel	2	378
Da'ar OB, 2018 [33]	2011	KSA (SAU)	Cancer	Not specified	2	10101
Da'ar OB, 2018 [34]	2016	KSA (SAU)	Not specified	The economic worth of dental residency training	20	169
Hayajneh WA, 2018 [35]	2016	Jordan (JOR)	Hepatitis A	Hepatitis A vaccination	26	8117564
Nuhoho S, 2018 [36]	2016	UAE (ARE)	Schizophrenia	Paliperidone palmitate	27	Not specified
Malik R, 2017 [37]	Not specified	KSA (SAU)	Glaucoma	National screening program	1	Not specified
Alsaqa'aby MF, 2017 [38]	2015	KSA (SAU)	Multiple sclerosis	Oral agents (fingolimod, teriflunomide, dimethyl fumarate) vs interferon	9	1000
Rudgard WE, 2017 [39]	2013	Yemen (YMD)	Tuberculosis	Cash transfer strategies to prevent catastrophic payments	3	320
Alonso S, 2017 [40]	2014	Morocco (MAR)	Leishmaniasis	Diagnostic and therapeutic strategies	6	100
Assefa Y, 2017 [41]	2016	Egypt (EGY)	Hepatitis C	Sofosbuvir differential pricing and licensing	6	830600
Razgallah Khrouf M, 2017 [42]	2013	Tunisia (TUN)	Hematologic diseases	Hematopoietic stem cell transplantation	24	32
Arafa MA, 2017 [43]	2016	KSA (SAU)	Prostate cancer	Screening in a low prevalence population	1	2898
Alefan Q, 2017 [44]	2014	Jordan (JOR)	Colorectal cancer	Colorectal cancer treatment: drugs, diagnostic,treatment, follow-up,rehabilitation, and hospitaladmission	38	97

Al-Otaibi H, 2017 [45]	Not specified	KSA (SAU)	Diabetic-retinopathy	Validity, Usefulness and Cost of screening	3	400
Mohammed WE, 2017 [46]	2016	Egypt (EGY)	Benign uterine diseases	Vaginal vs laparoscopic hysterectomy	2	50
El-Khamery AA, 2017 [47]	2014	Egypt (EGY)	Glaucoma	Monotherapy options	6	20
Al-Aidaros AYA, 2017 [48]	2012	KSA (SAU)	Rotavirus	Rotavirus vaccination	6	562428
Mustafa G, 2017 [49]	2013	Multi incl MENA	Middle ear infection	Incidence and economic burden of acute otitis media in children aged up to 5years	8	4043
Hassan A, 2017 [50]	2015	Egypt (EGY)	Polycystic ovarian syndrome	Treatment with letrozole vs. purified urinary FSH	2	140
Islam SM, 2016 [51]	2010	Oman (OMN)	Not specified	na	12	642
Khalifa M, 2016 [52]	2015	KSA (SAU)	Not specified	Exploring Lab Tests Over Utilization	2	6375
Cheikh A, 2016 [53]	2013	Morocco (MAR)	Cervical cancer	Evaluation of the cost of cervical cancer	15	550
Al-Ahmad M, 2016 [54]	2014	Kuwait (KWT)	Urticaria	Omalizumab	39	1293
Iyengar S, 2016 [55]	2015	Multi incl MENA	Hepatitis C	Sofosbuvir	2	Not specified
Hamidi S, 2016 [56]	2014	UAE (ARE)	Psychiatric disorders	Insurance plans and cost sharing patterns	25	Not specified
Hammad EA, 2017 [57]	2015	Jordan (JOR)	Not specified	Not specified	173	Not specified
El-Hamamsy MH, 2016 [58]	2014	Egypt (EGY)	Heart valve prosthesis	Warfarin with Low-dose Aspirin Versus Warfarin Alone	22	316
Bener A, 2016 [59]	2014	Qatar (QAT)	Diabetes mellitus	DM treatments (exercise or diet, taking oral medications only, taking insulin only and taking	57	2717

				both insulin and oral medications), disease control, complications and comorbidities		
Al-Badriyeh D, 2016 [60]	2014	Qatar (QAT)	Not specified	Proton pump inhibitors selected with multi-criteria decision analysis	4	100000
de Cuevas RM, 2016 [61]	Not specified	Multi incl Yemen (YMD)	Tuberculosis	Patients direct costs to undergo TB diagnosis	35	2225
Ahmad AS, 2016 [62]	2014	Oman (OMN)	Other circulatory diseases	Do not resuscitate policies	6	50
Faraj C, 2016 [63]	2013	Morocco (MAR)	Leishmaniasis	Insecticide-treated bed nets & indoor residual spraying for prevention	4	Not specified
Hyassat D, 2015 [64]	2013	Jordan (JOR)	Diabetes mellitus	premixed human insulin BHI30	2	628
Joosub I, 2015 [65]	2013	KSA (SAU)	Not specified	Imipenem cilastatin vs meropenem	34	88
Sadat-Ali M, 2015 [66]	2013	KSA (SAU)	Osteoporosis	na	3	157764
Sabry N, 2015 [67]	2013	Egypt (EGY)	Postoperative pain	Intravenous to oral paracetamol switch	28	Not specified
Soltani MS, 2015 [68]	2008	Tunisia (TUN)	Rotavirus	Epidemiology and medical cost of hospitalization	11	279
Alhelali RA, 2016 [69]	2013	KSA (SAU)	Pulmonary disease	Home respiratory therapy services	4	83
Al Alawi S, 2015 [70]	2014	Bahrain (BHR)	Pharyngitis	Outpatient parenteral ceftriaxone	3	97
Al-Badriyeh D, 2015 [71]	2014	Qatar (QAT)	Hypercholesterolaemia	Statin Selection in Multi-indication Pharmacotherapeutic Multi-criteria Scoring Model	5	100000
Estes C, 2015 [72]	2015	Egypt (EGY)	Hepatitis C	Population treatment scenarios	10	Not specified
Al-Kaabi SK, 2015 [73]	2013	Qatar (QAT)	Not specified	Impact of noncommunicable diseases in the State of Qatar	3	Not specified

Bouassida M, 2016 [74]	2008	Tunisia (TUN)	Cholecystitis	The management of acute cholecystitis	2	649
Nasef SA, 2015 [75]	2013	KSA (SAU)	Osteoarthritis	Celecoxib versus non-steroidal anti-inflammatory drugs plus proton-pump inhibitors	35	Not specified
Sibak M, 2015 [76]	2013	Egypt (EGY)	Pneumococcus	Pneumococcus vaccination	31	Not specified
El Sabaawy D, 2015 [77]	2012	Egypt (EGY)	Hepatitis C	Pegylated interferon alpha variates	8	60
Younis M, 2015 [78]	2012	Palestine (PSE)	Renal failure	Transplant versus hemodialysis	10	692
Alkoshi S, 2015 [79]	2013	Libya (LBY)	Rotavirus	Rotavirus vaccines	11	140
Al Quran HA, 2015 [80]	2014	Jordan (JOR)	Skin diseases	Real-time teledermatology	2	88
Eltabbakh M, 2015 [81]	2011	Egypt (EGY)	Hepatocellular carcinoma	Screening program	22	1286
Alkoshi S, 2014 [82]	2012	Libya (LBY)	Rotavirus	Rotavirus vaccination	28	311
Kim DD, 2015 [83]	2014	Egypt (EGY)	Hepatitis C	Screening and treatment program	26	Not specified
Aburahma SK, 2015 [84]	2011	Jordan (JOR)	Epilepsy	Vagus nerve stimulation	5	28
Gupta V, 2015 [85]	2013	KSA (SAU)	Diabetes mellitus	Switch to biphasic insulin aspart 30 from other insulin preparations	24	680
Home P, 2015 [86]	2013	Algeria (DZA)	Diabetes mellitus	Insulin detemir	20	Not specified
Alzaabi A, 2014 [87]	2011	UAE (ARE)	Asthma	Treatment of asthma	11	139092
Shafie AA, 2014 [88]	2013	Multi incl MENA	Diabetes mellitus	Biphasic insulin aspart 30	16	KSA(90 1) & DZA,TU N, MAR(27 9)

Assanelli D, 2015 [89]	2008	Algeria (DZA)	Cardiac arrest	ECG screening	14	1071
Al-Qadhi W, 2014 [90]	2012	KSA (SAU)	Depression	Screening program	13	477
Wilcox ML, 2015 [91]	2010	Syria (SYR)	Coronary heart diseases	Salt reduction policy for prevention	6	Not specified
Al Awaidy ST, 2014 [92]	2010	Oman (OMN)	Rotavirus	Rotavirus vaccination	27	65500
Shehab H, 2014 [93]	2012	Egypt (EGY)	Hepatitis C	A Hansenula-Derived 20 kDa Pegylated Interferon Alpha-2a	2	193
Obach D, 2014 [94]	2012	Egypt (EGY)	Hepatitis C	Peginterferon biosimilar+ribavirin48w / sofosbuvir+ peginterferon biosimilar + ribavirin 12w by fibrosis stage	16	Not specified
Haddad NS, 2014 [95]	2011	Iraq (IRQ)	Diabetes mellitus	Short message services (SMSs) to support Iraqi adults with newly diagnosed type 2 diabetes	1	50
El-Meteini M, 2014 [96]	Not specified	Egypt (EGY)	Liver diseases	Living Donor Liver Transplantation	5	66
Mason H, 2014 [97]	2010	Multi incl MENA	Coronary heart diseases	Salt reduction policy for prevention	87	Not specified
Alkoshi S, 2014 [98]	2012	Libya (LBY)	Rotavirus	Rotavirus vaccination	16	160000
Kim JJ, 2013 [99]	2010	Extended Middle East & North Africa (EMENA)	Cervical cancer	HPV vaccination (cervical cancer prevention)	7	Not specified
Aljbouri TM, 2013 [100]	2010	Jordan (JOR)	Not specified	Clinical pharmacist	4	Not specified
Bawazeer AM, 2013 [101]	2010	KSA (SAU)	Uveitis	Prevalence of HLA-B27-related uveiti in eastern countries	2	330

Almutairi N, 2013 [102]	2011	KSA (SAU)	Diabetes mellitus	Direct Medical Cost and Glycemic Control	24	300
Al-Sharayri MG, 2013 [103]	2012	Jordan (JOR)	Diabetes mellitus	Insulin vial	2	556
Algahtani F, 2013 [104]	2010	KSA (SAU)	Deep vein thrombosis	Home vs hospital treatment with low molecular weight heparin	10	61
Khan SY, 2013 [105]	2012	Oman (OMN)	Appendicitis	Laparoscopic vs open appendectomy	12	109
Al-Busaidi NH, 2013 [106]	2010	Oman (OMN)	Asthma	The asthma cost	21	147072
Tuma MA, 2013 [107]	2008	Qatar (QAT)	Injury	Trauma care	9	281
AlBedah AM, 2014 [108]	2011	KSA (SAU)	Not specified	Costs of tobacco consumption	2	Not specified
Sutherland T, 2013 [109]	2010	Egypt (EGY)	Intrapartum haemorrhage	Non-pneumatic anti-shock garment	20	1000
Barakat A, 2013 [110]	2005	Egypt (EGY)	Diarrhea	Children with diarrhea	9	763
Younis MZ, 2013 [111]	2008	Palestine (PSE)	Not specified	Not specified	81	Not specified
Al-Omar HA, 2013 [112]	2002	KSA (SAU)	Not specified	Not specified	3	20521
Berraho M, 2012 [113]	2008	Morocco (MAR)	Cervical cancer	Cervical Cancer Management	45	900
Bennis I, 2012 [114]	2010	Morocco (MAR)	Cesarean section	Fee exemption policy	16	100
Khadadah M, 2013 [115]	2010	Kuwait (KWT)	Asthma	Asthma	24	143462
Tachfouti N, 2012 [116]	2012	Morocco (MAR)	Lung cancer	na	16	3336
Connolly MP, 2012 [117]	2009	Egypt (EGY)	Rotavirus	Rotavirus vaccination	4	1909000

Othman GQ, 2012 [118]	2009	Yemen (YMD)	Tuberculosis	Costs associated with tuberculosis (TB) diagnosis and treatment for the public health services and patients	52	320
Alameddine M, 2012 [119]	2010	KSA (SAU)	Bladder cancer	To determine whether urine cytology is still essential in the work up of suspected urothelial cancer patients and to measure its cost-effectiveness	1	563
Alkire BC, 2012 [120]	2008	Algeria (DZA), Libya (LBY), Morocco (MAR), Oman (OMN), Tunisia (TUN), Yemen (YMD)	Cesarean section	Cesarean section	12	Not specified
Al-lela OQ, 2012 [121]	2014	Iraq (IRQ)	Not specified	Evaluation in terms of time and cost	35	528
Abuelkhair M, 2012 [122]	2004	UAE (ARE)	Not specified	Generic prescription policy (proton pump inhibitors, statins, ezetimibe)	27	Not specified
Al Saran K, 2012 [123]	2010	KSA (SAU)	Renal failure	Hemodialysis cost assessment	33	≈200
Mabrouk A, 2012 [124]	Not specified	Egypt (EGY)	Burns	Aquacel vs MEBO	2	40
Younis MZ, 2011 [125]	2003	Palestine (PSE)	Not specified	Cardiac Catheterization Services	7	1743
Shafie KE, 2010 [126]	2007	Oman (OMN)	Thyroid disease	Pts screening for thyroid disease	1	319
Gheith OA, 2011 [127]	2005	Egypt (EGY)	Renal failure	Steroid-free immunosuppression in renal transplantation	24	100
Khoury H, 2011 [128]	2008	MENA & Turkey	Rotavirus	To estimate the burden of RVGE	1	Not specified

Hajr E, 2011 [129]	2009	KSA (SAU)	Not specified	Suction cautery adenoidectomy (SCA)	2	86
Al-Maskari F, 2010 [130]	2004	UAE (ARE)	Diabetes mellitus	Assessment of the direct medical costs of diabetes mellitus and its complications	62	150
Sladkevicius E, 2010 [131]	2007	Libya (LBY)	Phenylketonuria	Screening program	35	Not specified
Boutayeb S, 2010 [132]	2007	Morocco (MAR)	Breast cancer	Trastuzumab & taxanes for treatment of early breast cancer	20	5500
Denewer A, 2010 [133]	2010	Egypt (EGY)	Breast cancer	Mammography	4	5900
Younis MZ, 2010 [134]	2007	Palestine (PSE)	Not specified	A multi-service hospital	91	43787
Ramsay A, 2010 [135]	Not specified	Egypt (EGY)	Breast cancer	Clinical Breast Assessment-Based Screening	4	5900
Younes M, 2010 [136]	2006	Tunisia (TUN)	Ankylosing spondylitis	Socioeconomic impact of ankylosing spondylitis	23	50
Ortega O, 2009 [137]	2005	Egypt (EGY)	Rotavirus	Rotavirus vaccination	15	56
Al Awaidey SA, 2009 [138]	2008	Oman (OMN)	Rotavirus	Rotavirus Vaccine	5	1712
El-Karakasy H, 2008 [139]	2004	Egypt (EGY)	Liver diseases	Prescreening versus empirical vaccination for hepatitis A	5	172
Sabry A, 2009 [140]	Not specified	KSA (SAU)	Renal failure	Low-molecular-weight vs unfractionated heparins in hemodialysis	2	23
El-Zawahry HM, 2007 [141]	2002	Egypt (EGY)	Acute myeloid leukemia	Conventional chemotherapy (CCT)	31	82
Mitwalli AH, 2001 [142]	Not specified	KSA (SAU)	Renal failure	Dialyser reuse	2	10
Al-Mueilo SH, 2005 [143]	1999	KSA (SAU)	Renal failure	Intravenous iron saccharate in dialysis	2	34

Eldaly M, 2007 [144]	Not specified	Egypt (EGY)	Glaucoma	Intraocular pressure (IOP)-lowering medications	3	68
Al-Siyabi K, 2007 [145]	2003	Oman (OMN)	Not specified	To examine the value and types of medicines returned by patients	2	381
Rkain H, 2007 [146]	2006	Morocco (MAR)	Ankylosing spondylitis	Not specified	1	100
Al-Kaisy AA, 2006 [147]	Not specified	Iraq (IRQ)	Burns	Zinc supplement	2	58
Nagi MA, 2005 [148]	2001	Yemen (YMD)	Schistosomiasis	Infection control programme (chemotherapy and education)	19	863
Al-Inany HG, 2006 [149]	2005	Egypt (EGY)	Infertility	Human menopausal gonadotrophin vs recombinant follicle stimulating hormone for ovulation induction	14	100000
Rkain H, 2006 [150]	Not specified	Morocco (MAR)	Rheumatoid arthritis	Socioeconomic impact of rheumatoid arthritis	5	100
Lahiri S, 2005 [151]	2000	Egypt (EGY); Iraq (IRQ), Morocco (MAR), Yemen (YMD)	Back pain	Training, engineering controls, and a comprehensive full ergonomics program	44	Not specified
Mawajdeh S, 2004 [152]	2001	Jordan (JOR)	Not specified	Rationalising primary care staff	92	Not specified
Aasham T, 2004 [153]	2003	Oman (OMN)	Hearing loss	Audiometric screening	7	Not specified
Curtale F, 2005 [154]	2000	Egypt (EGY)	Fascioliasis	School-based infection control program (selective chemotherapy)	23	10739
Al-Kaisy AA, 2005 [155]	2003	Iraq (IRQ)	Burns	Vitamin e with vitamin C and topical povidone-iodine ointment	5	28

Majorowski MM, 2005 [156]	2000	Tunisia (TUN)	Echinococcosis	A cost analysis	4	Not specified
Morris RE, 2004 [157]	1998	Kuwait (KWT)	Dental caries	Oral health program	2	Not specified
Fateha BE, 2001 [158]	1999	Bahrain (BHR)	Injury	Triage	1	Not specified
Al-Zakwani I, 2003 [159]	2000	Oman (OMN)	Epilepsy	The antiepileptic drug (AED) lamotrigine and specialist visits	9	486
Almuneef M, 2003 [160]	2003	KSA (SAU)	Varicella	Health care workers Varicella zoster virus immunity	4	Not specified
Abou-Auda HS, 2003 [161]	2001	KSA (SAU)	Not specified	Economic Assessment of the Extent of Medication Use and Wastage Among Families	13	1641
Vassall A, 2002 [162]	1999	Syria (SYR)	Tuberculosis	Infection control strategies (Directly observed treatment, short-course; DOTS)	51	285
Yip W, 2001 [163]	1995	Egypt (EGY)	Not specified	School health insurance program	5	17170
Talaat M, 2000 [164]	1997	Egypt (EGY)	Schistosomiasis	Infection control programs	1	30440
Al-Dawood K, 2000 [165]	Not specified	KSA (SAU)	Injury	The incidence rate of non-fatal occupational injuries	1	65915
Al-Tawfiq JA, 2010 [166]	2008	KSA (SAU)	Pneumonia	Health improvement bundle	1	Not specified
Atiyeh BS, 2002 [167]	Not specified	Egypt (EGY)	Burns	Moist exposed burn ointment MEBO	32	36
Ali M, 2008 [168]	2007	KSA (SAU)	Diabetes mellitus	Biphasic insulin aspart 30 (BIAsp 30)	36	598
Mammo L, 2006 [169]	Not specified	KSA (SAU)	Not specified	Comparison between the Light Cycler® and the PCR-restriction fragment length polymorphism in detecting factor V Leiden	16	2131

				and factor II 20210G>A mutations		
Abbas M, 2006 [170]	2003	KSA (SAU)	Influenza	Workplace influenza vaccinations	35	2400
Pejaver RK, 2001 [171]	Not specified	KSA (SAU)	Respiratory distress	Surfactant replacement therapy	16	≈150
Qari FA, 2001 [172]	2000	KSA (SAU)	Thyrotoxicosis	Outcome of thyrotoxicosis treatment	5	100
Jawad AJ, 1998 [173]	Not specified	KSA (SAU)	Cholelithiasis	Cost Analysis and Review of Current Indications : laparoscopic cholecystectomies	2	18
Alangari AA, 2008 [174]	2005	KSA (SAU)	Not specified	To evaluate the effect of intravenous immunoglobulin (IVIG) utilization at King Khalid University Hospital	9	305
Jawadi AH, 2007 [175]	2005	KSA (SAU)	Injury	Fixation of femoral fracture using intramedullary Kirschner wire	1	178
Al Khabori M, 2007 [176]	1996	Oman (OMN)	Impacted cerumen	Diagnosis and management of impacted wax	17	11402
Howidi M, 2012 [177]	2010	UAE (ARE)	Gastroenteritis	Pediatric acute gastroenteritis	7	500
Ahmad S, 2014 [178]	Not specified	Kuwait (KWT)	Not specified	Low-Cost Molecular Assays for TR 34/L98H Mutations	1	75
Al Balushi KA, 2013 [179]	2012	Oman (OMN)	Not specified	Drug prescription trends in emergency department	22	300
Salem K, 2017 [180]	2015	KSA (SAU)	Heart failure	Gender-adjusted and age-adjusted economic inpatient burden	19	174
Hindawi S, 2018 [181]	2015	KSA (SAU)	Not specified	Testing for HTLV 1 and HTLV 2 among blood donors	2	107419
Schubert A, 2017 [182]	2016	UAE (ARE)	Diabetes mellitus	Evaluating the costs of glycemic response with canagliflozin versus	10	Not specified

				dapagliflozin and empagliflozin		
Harwan WA, 2014 [183]	2012	Egypt (EGY)	Pneumonia	Antibiotic combination regimen containing fluoroquinolone	24	7
Abdel-Raheem TA, 2016 [184]	2013	Egypt (EGY)	Scabies	Evaluate four drug regimens for treatment of scabies	4	200
Elsisi GH, 2017 [185]	2016	Egypt (EGY)	Hepatitis C	Anemia management	34	220000
Hamidi S, 2008 [186]	2000	Palestine (PSE)	Not specified	Implementing an essential medicines list	31	Not specified