Lung cancer is the second-most prevalent cancer and, the most common cause of cancer-related mortality throughout the world. Evidence-based strategies to decrease its incidence and mortality are being implemented in different parts of the world. Smoking cessation policies are being actively publicized to decrease the incidence of tobacco related cancers including lung cancer. Screening program for early detection of localized lung cancer which can then be targeted by a multimodality approach utilizing surgery, radiation, chemoimmunotherapy to achieve cure is now becoming the standard in several high-income countries. Precision medicine in lung cancer is booming with metastatic non-curative cancers targeted with small molecule tyrosine kinase inhibitors. However, these advancements are not available all around the world. Inequalities exist in the management of lung cancer, mostly driven by the economic differences between the countries. Raising awareness to these international barriers is pivotal for improving lung cancer related incidence and mortality.

Take home message

- Almost 60% of lung cancer incidence throughout the world is seen in the low- and middle-income countries.
- Several disparities exist in the screening, diagnostics, and management of lung cancer in the low- and middle-income countries when compared to the high-income countries.
- Limited resources, economic restrictions, and lack of accessibility are the major causes for the differences seen in the management of lung cancer in the low- and middle-income countries.
- Understanding the local limitations and implementing innovative strategies to overcome these problems can help bridge the worldwide gap seen in the management of lung cancer.

1. INTRODUCTION

The field of thoracic oncology witnessed immense growth in the last two decades. From the development of effective lung cancer screening guidelines which aim for an early diagnosis of asymptomatic and non-metastatic lung cancers to the advent of immunotherapy and targetable tyrosine kinase inhibitors which aim to improve the quality of life and survival in metastatic lung cancer patients, several breakthroughs have been made. However, lung cancer remains the most common cause of cancer-related mortality despite all the advances, accounting for about 1.8 million deaths worldwide in 2020. Several inequalities exist in managing lung cancer worldwide, which ultimately contribute to the disparities in its incidence and mortality burden. One commonly encountered reason for these inequalities is the socio-economic variations in the different parts of the world. The World Bank list of economies divides the countries into four sub-groups based on their Gross National Income (GNI) per capita- low income, lower-middle income, upper-middle income, and high income. Among the low- and middle-income countries, the age-standardized incidence and mortality are highest in Micronesia (36.4% and 34.9%, respectively) and Eastern Asian countries (34.4% and 28.1%, respectively), while its lowest in the Western-African region (2.2% and 2.1% respectively). Overall, about 60% of the world’s lung cancer incidence is attributed to low- and middle-income countries, with the majority noted in the Asian continent. Hence, recognizing the challenges faced by the patients and physicians in these countries is essential to improve the global outcomes of lung cancer.

2. HEALTHCARE SYSTEM

Healthcare is divided into public and private sectors in most low- and middle-income countries. The government primarily sponsors public sector hospitals/universities, and they provide care to the patients at a low cost; however,
most advanced diagnostics, procedures, and novel medica-
tions might not be readily available in these hospitals due
to their cost limitations. The private sector hospitals tend
to have an underlying for-profit motive. Though they have
more access to the newer products, their use in public is
limited to high-income or privately insured patients. Ex-
cept for some upper-middle-income countries like China
and Mexico, and a few lower-middle-income countries like
Vietnam, most of the low- and middle-income regions do
not have comprehensive nationally funded public health
insurance programs that are able to cover the expensive
testing and treatment required for lung cancer. Thus, pa-
tients must rely on private insurance or out-of-pocket pay-
ments which leads to financial toxicity.

3. SMOKING CESSATION

Tobacco use is suspected to have killed 8 million people in
2019 and is the most common risk factor for lung cancer
worldwide. The tobacco cessation efforts by WHO (FCTC,
NCD-GAP, MPower, and ENDS) have been instrumental
in controlling the tobacco epidemic. The fourth edition of
the WHO global report on the trends in the prevalence of
tobacco use reported a global decline in tobacco use from
32.7% in 2000 to 22.3% in 2020. Lower-middle income
groups had the highest drop in tobacco use (44% in 2000 to
24% in 2020), while the upper-middle income had the low-
est and slowest drop (28% in 2000 to 24% in 2020). How-
ever, some of South-East Asian and Middle Eastern coun-
tries like Myanmar, Indonesia, and Lebanon still have a
tobacco use prevalence as high as 50%. Primary and sec-
ondary smoking abstinence has been shown to be asso-
ciated with improved survival outcomes. In the National
Lung Cancer Screening trial, there was a 20% reduction
in cancer-related mortality with 7-year smoking cessation.
Despite the awareness and the evidence, there are about
49 countries that currently do not have a single national
control measure, and a majority of them belong to low-
and middle-income countries. In addition to cigarette use,
other causes of nicotine exposure commonly encountered
in low- and middle-income countries include second-hand
tobacco smoke and the use of non-cigarette nicotine prod-
ucts like beedi, toombak. These products are generally
cheaper and cause higher nicotine exposure.

The incidence of lung cancer in non-smokers is increas-
ing globally. Majority of the Asian women with lung cancer
are non-smokers. Some of the risk factors for lung cancer
that have been proposed in this population are outdoor air
pollution, environmental exposures (arsenic, asbestos), ge-
netic factors, benign pulmonary conditions (pulmonary fi-
brosis) etc. In rural areas of India, indoor air pollutants
like smoke from coal stoves and cooking oil have been at-
tributed to lung cancer as well. Further case-control stud-
ies to help establish a definite causal relationship with
these non-smoking factors is essential.

4. LUNG CANCER SCREENING

Wilson and Jungen laid ten principles for disease
screening in 1968, which are still used while deciding on
screening recommendations for cancers. Lung cancer bi-
ology and epidemiology make it a disease that would highly
benefit from screening. The United States National Lung
Screening Trial (NLST) and the Dutch-Belgian NEDernlands
Leuvens Screening Onderzoek trial both demonstrated a
significantly reduced lung cancer-related mortality with
the use of annual low-dose CT screening in high-risk in-
dividuals. United States Preventive Service Task Force
(USPSTF) currently recommends LDCT for lung cancer
screening in high-risk patients in the United States of
America.

The majority of the low- and middle-income countries
with a high incidence of lung cancer, like India, Bangladesh,
and Vietnam currently do not have screening guidelines
established for lung cancer. In most low- and middle-in-
come countries, nearly 80% of lung cancers are diagnosed
as stage III or IV. Mortality in lung cancer is stage-depen-
dent, with stage IV having the worst outcomes. Hence,
early detection of lung cancer with the help of screening
modalities can help decrease mortality. However, in practi-
cality, several barriers exist for an effective implementation
of lung cancer screening. A high prevalence of pulmonary
infections like tuberculosis results in a high false positive
rate. A positive screening test must be followed with sev-
eral invasive and non-invasive interventions to ultimately
lead to an accurate diagnosis. The imaging and interven-
tional modalities needed for lung cancer screening can add
to the already existing financial and infrastructure burden
in the low- and middle-income healthcare systems.

5. MANAGEMENT OF NON-METASTATIC LUNG
CANCER

The goal of treatment for non-metastatic lung cancer is the
cure, primarily obtained with surgery or with definitive ra-
diation in patients who are not surgical candidates. Adju-
vant systemic therapy is added to stage II and III lung can-
cers to improve the cure and survival rates.

**Surgery:** Anatomic surgical resection (lobectomy and
sometimes pneumonectomy) is the most common surgical
procedure that is performed for an early-stage lung cancer
with curative intent. The lung resection surgery can be per-
formed via open thoracotomy, video-assisted thoracoscopic
surgery (VATS) or robotic-assisted thoracoscopic surgery.
While VATS and RATS are associated with faster recovery
and lesser post-operative complications, there is no dif-
ference in cancer related survival outcomes compared to
open thoracotomy. When surgical resection is indicated,
open thoracotomy is the most commonly used approach in
most low- and middle-income countries. VATS is being
increasingly used in countries like Brazil and Vietnam.
RATS is less commonly available in most of these coun-
tries except for China, where robotic technology is rapidly
advancing. In countries with a high incidence of pul-
monary infections, like India and Nepal, there is a concern
for increased lung fibrosis and pleural adhesions making minimally invasive surgical resection less feasible.\textsuperscript{26} The availability of skilled surgical oncologists or thoracic surgeons and post-operative rehabilitation resources differ widely throughout the world. The disparities in resource availability results in lower surgical resection rates; however, the overall post-operative outcomes are similar to high-income countries.\textsuperscript{27}

**Radiotherapy (RT):** For stages I and II non-small cell lung cancer (NSCLC), definitive RT is used in patients who are not surgical candidates. In inoperable stage III tumors, it is used along with chemotherapy (concurrent or sequential). In stage IV lung cancer, it is used for treatment of brain metastasis or oligo-progression or symptomatic disease. In limited-stage small-cell lung cancer (SCLC), prophylactic cranial radiation is given following concurrent chemoradiation to the chest.\textsuperscript{15} Hence, radiotherapy is a vital part of treatment for all stages of lung cancer management. The availability of radiotherapy equipment and techniques is variable in each country. In general, there is a paucity of RT availability in low- and middle-income countries. For example, India has radiotherapy equipment to serve only half of its current population.\textsuperscript{38} Furthermore, only bigger cities within each country have established radiotherapy centers, making it difficult for the rural population to use them. Additionally, patients have a high wait time to receive RT due to limited availability. For instance, the average wait time for radiotherapy in Brazil is about 3–4 months.\textsuperscript{22} This can often result in the progression of the disease from a curative to non-curative stage or can cause the development of symptomatic metastasis intra- and extracranially.

6. MANAGEMENT OF METASTATIC LUNG CANCER

Metastatic lung cancer is treated primarily with systemic agents to help improve quality of life, progression-free survival, and overall survival. The goal of treatment is palliative and not curative. Hence, it remains the most common cause of lung cancer-related mortality worldwide, with an average 5-year survival of 5–7\% in the United States of America.\textsuperscript{29} The systemic treatment in lung cancer underwent radical progress in the last decade with the dawn of immunotherapy and targetable tyrosine kinase inhibitors which are now readily available for patients in the high-income countries like the North American and European countries. However, most of the major clinical trials that led to the approval of these agents (especially immunotherapy trials) had minimal to no accrual from the low- and middle-income countries located in the Middle East, South Asia, and North and South African regions. This lack of inclusivity precipitates a lack of awareness, availability, and accessibility which along with the high economic burden results in lower utilization of these novel agents in low- and middle-income countries.

**Tyrosine Kinase Inhibitors (TKI):** Understanding the oncogenic drivers and targeting them with small molecule TKI revolutionized the management of non-small cell lung cancer (NSCLC). However, TKI use in most low- and middle-income countries is limited due to the lack of comprehensive molecular testing, lack of access to several TKIs, and the cost of the medication. It is thought that less than 50\% of patients with NSCLC throughout the world receive molecular testing,\textsuperscript{30} and the most commonly cited reasons for under testing are lack of availability/access and the cost. In Brazil, EGFR evaluation is estimated to be used in only half of the metastatic NSCLC due to the lack of advanced diagnostics.\textsuperscript{22,31} In Nepal, the samples for comprehensive testing are sent to India and are generally associated with high expenses.\textsuperscript{26} Like testing, there is also a stark difference in the availability of TKIs between high-income and low-income countries. Currently, several TKIs targeting EGFR, ALK, ROS, NTRK, BRAF, MET, RET, and most recently, KRAS G12C are approved and available in the USA and Europe. Out of all these mutations, EGFR is the most commonly encountered targetable mutation in NSCLC, with prevalence much higher in the East Asian population (EGFR mutation is noted in about 15\% of NSCLC patients in the USA while it’s frequency can be as high as 60\% in East Asian countries).\textsuperscript{52} China is one of the few Asian countries in the upper-middle-income group that actively participated in several TKI studies and currently has access to multiple TKIs targeting EGFR mutation, including Osimertinib.\textsuperscript{35} However, the same cannot be said about the rest of South-East Asian countries. In Malaysia and Vietnam, Erlotinib and Gefitinib are the only available EGFR–TKIs in the public sector with reduced costs and national reimbursements. The rest of the EGFR TKIs must be fully paid for by the patients. The out-of-pocket monthly cost of Osimertinib is about 2000\$ in Malaysia and 8000\$ in India/Brazil.\textsuperscript{34} A similar trend is seen with TKIs targeting mutations other than EGFR, with monthly costs ranging from 2000\$ to 10,000\$.\textsuperscript{28} Hence, their use is limited as a second-line treatment for affluent patient populations in the tertiary healthcare systems.\textsuperscript{33,35}

**Immunotherapy (IO):** In the non-oncogene-addicted metastatic NSCLCs, an addition of immunotherapy significantly improved response rates and survival outcomes when compared with standard chemotherapy.\textsuperscript{36–39} Similarly, in small cell lung cancer (SCLC), an addition of immunotherapy to chemotherapy improved OS and PFS irrespective of PDL1 immunohistochemistry.\textsuperscript{40,41} Immunotherapy is also responsible for producing a durable clinical benefit.\textsuperscript{18,42} Currently, atezolizumab and durvalumab (PDL-1 inhibitors) are FDA approved for metastatic SCLC and, atezolizumab, pembrolizumab, cemiplimab (PD1 inhibitors) and nivolumab/pilimumab (PD-1/CTLA4 inhibitor combination) are approved for metastatic NSCLC.\textsuperscript{15} Immunotherapy is also recommended in non-metastatic NSCLC. Durvalumab significantly improved survival in stage III NSCLC when given following chemoradiation.\textsuperscript{43} Atezolizumab in the adjuvant setting improved disease-free survival for PDL-1 positive resectable stage II and IIIA NSCLC.\textsuperscript{44} Additionally, neoadjuvant nivolumab in combination with chemotherapy has been shown to improve pathological complete response rates in resectable stage I to IIIA NSCLC.
Despite the ever-increasing evidence and indications for immunotherapy in high-income countries, their availability and utilization in low- and middle-income countries continue to remain low. Sudan does not have access to any immunotherapy agents or PDL-1 testing. In South Africa, no checkpoint inhibitors are available for first-line treatment and Pembrolizumab is the only available IO in the second-line setting. In India, IOs are sold as branded medications and have an average cost of 2000–4000$ per vial, which significantly restricts their use (especially in the first-line setting). Similar trends of restricting IO use to second-line setting are seen in most low- and middle-income countries in the Middle Eastern, North African (MENA), and Southeast Asian regions due to a financial burden. Owing to the lack of widespread global accessibility due to its cost, immunotherapy was not included in the essential medicine list by WHO.

Chemotherapy: Due to the cost and unavailability of most TKIs and IOs, platinum-based doublet chemotherapy remains the standard of care for first-line treatment of metastatic NSCLC and SCLC in low- and middle-income countries. In patients with NSCLC who have a driver mutation, every attempt is made to get cost-effective access to TKIs. In scenarios when the TKIs are unavailable or not affordable, chemotherapy is given in the first-line setting. There is not much discrepancy in the availability of most first- and second-line chemotherapy agents except for Pemetrexed which has limited availability in countries like South Africa and Malaysia.

SUMMARY AND PERSPECTIVE

In summary, every single aspect of lung cancer management, from epidemiologic risk mitigation to the availability of palliative treatment, is strongly influenced by the resources available in a country. These differences in the resources are often attributed to the financial burden of treatments, lack of accessibility and lack of awareness. Some of the potential solutions are:

1. Lung cancer prevention and screening: Implementing tobacco control policies like nicotine-replacement therapies, smoking-related cancer awareness campaigns and a nationwide ban on tobacco use in the public places can help decrease the prevalence of lung cancer. Use of plain packaging and graphic pictorial warnings on nicotine products has been shown to decrease their attractiveness especially to young population and hence, wider implementation of these measures as suggested by WHO can help with smoking cessation. New Zealand recently announced national plans to ban tobacco products for anyone born after 2008. Similar age-based restrictions on nicotine use can target the youth and decrease the incidence of tobacco use. Hiking the prices of tobacco products can decrease their use as well. In addition to smoking cessation, starting a screening program can help reduce the long-term cancer-related mortality. Socio-economic burden is the biggest challenge in providing appropriate screening in the low- and middle-income countries, however, cultural concerns and fear of radiation exposure can also rarely lead to its underutilization. Hence, investigating to understand the local population’s outlook towards lung cancer screening and raising awareness utilizing national media can help deploy a successful screening program. Though these measures can increase the immediate cost of healthcare, focusing on lung cancer prevention and early detection can be cost-effective for a nation in the long run.

2. Clinical trials: There is an abundance of lung cancer patients in low- and middle-income countries who fit the general inclusion criteria noted in most lung cancer clinical trials. However, their inclusion in most trials is dismal. Through clinical trials, patients can get access to molecular testing and novel treatments like TKIs and CPIs at minimal to no cost.

3. National health insurance coverage: The population within each country is divided into multiple tiers based on individual income. Patients from high-income families can afford out-of-pocket payments or private insurance. On the other hand, patients from low-income households can rarely afford cancer treatments without almost bankrupting their families. Hence, having a nationally funded health insurance that works towards providing basic medical care including coverage to the well-acknowledged diagnostics and cancer treatments can result in uniform oncologic care. In addition to national provisions, state-based monetary help and hospital-based medical coverage for cancer patients as seen in certain states/hospitals of India can bridge the economic gap often seen in cancer care.

4. National cancer/disease registries: A national cancer registry can provide information on the most prevalent cancers and their mortality in each country. This can further help concentrate funds and resources on the cancer types that are adding the most social and economic burden on the country and its population. International investigators can also use this registry while considering clinical trial accrual.

5. National guidelines for management: Several low- and middle-income countries like Sudan, Nepal, and Georgia do not have national consensus guidelines for managing lung cancer and rely on National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines. NCCN has harmonized guidelines for countries in the Sub-Saharan Africa, the Middle East, North Africa, and the Caribbean regions. However, there are no international guidelines that are focused on managing cancer for patients from South Asia, South-East Asia, Pacific Islands, and Latin America, which also have several low- and middle-income countries. Establishing national guidelines for managing lung cancer can help provide uniform care to patients within each country. Once these guidelines are made publicly available throughout the country, then, the insurance providers (both public and private
6. Teleoncology: Utilization of digital technologies like Telemedicine became essential during the pandemic era. In the low- and middle-income countries where the majority of the burden falls on the tertiary care hospitals, appropriate use of Teleoncology can reduce delay in oncologic care by triaging patients for screening, lab tests or invasive diagnostics. It can also help in patient counseling and surveillance.

7. Cost of the medication: The most encountered barrier to appropriate treatment in low- and middle-income countries is the cost of the treatment. Increasing the availability of bio-equivalent drugs can help decrease their expense. TKIs like gefitinib and alectinib are available as generic agents in India, which decreased the cost of the medication by almost half for the consumers. Doing the same for several TKIs and immunotherapy can help increase their affordability. Another important potential solution is the use of lower doses of therapeutic agents, especially immunotherapy to help mitigate their financial toxicity. A recent phase III trial from India showed improved survival in Head and Neck cancer with a combination of Nivolumab given at 6% of the recommended dose along with metronomic doses of chemotherapy drugs. The possibility of ultra-low doses of anti-cancer drugs providing similar efficacy in Lung cancer needs to be further explored as it can help significantly decrease the total cost of the treatment.

CONFLICT OF INTEREST
None.

FUNDING INFORMATION
N/A

ETHICAL STATEMENTS
N/A

ACKNOWLEDGEMENT
None

AUTHOR CONTRIBUTIONS
i. All authors: conception and design
ii. All authors: data collection and assembly
iii. All authors: data analysis, manuscript writing

All authors have approved the manuscript

Submitted: January 08, 2023 PDT, Accepted: February 19, 2023 PDT
Figure 1. Age-standardized incidence and mortality rates of lung cancer; source WHO 2020 data

Figure 2. Summary of potential strategies to improve cancer-related treatment access and outcome
REFERENCES


