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Score to Save: Revolutionizing EsophagealCancer Screening with Multifaceted Indicators

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Abstract

Introduction
Esophageal cancer remains a signi cant global health concern, with challenges in early detection and screening. This study addresses the existing gaps in esophageal cancer screening by developing a scoring system utilizing eight key indicators: acid reux, gender, age,smoking (in pack years), alcohol consumption (beverages per week), location of residence, genetic predisposition, pre-existing gastroenterological conditions and obesity measured by BMI. The aim is to enhance the accuracy and e ciency of early detection through a multifaceted approach.

Material & Methods
Our methodology involved a rigorous meta-analysis of numerous studies published from 2013 to 2023 to identify the most reliable indicators for esophageal cancer risk. Data from diverse populations were synthesized, ensuring a comprehensive and representative analysis. The scoring system was developed through statistical modeling, assigning weights to each indicator based on their significance. The model's validity and reliability were assessed through cross-validation and comparison with existing screening methods.

Results The key findings reveal a robust scoring system that effectively integrates the selected indicators, providing a nuanced and accurate assessment of esophageal cancer risk. Notably, indicators such as acid reflux, smoking history, and genetic predisposition emerged as strong predictors. The model demonstrated superior sensitivity and specificity compared to current screening methods. Subgroup analyses highlighted variations in risk patterns across different demographics and geographic locations.

Conclusion
In conclusion, our research establishes a novel scoring system for esophageal cancer screening, utilizing a combination of eight indicators. This approach o ers a more nuanced and personalized risk assessment, potentially leading to earlier detection and improved outcomes.As we move forward, the integration of this scoring system into routine screening protocols holds promise for enhancing preventive strategies and reducing the burden of esophageal

cancer. Future perspectives include prospective validation studies and continuous renement of the scoring system based on emerging research and technological advancements.

Introduction

Esophageal cancer remains a significant global health concern, with challenges in early detection and screening. It ranks as the eighth most commonly diagnosed cancer and the sixth leading cause of cancer death globally. [1] [2] This malignancy predominantly affects less developed regions, accounting for nearly 80% of cases. Approximately 70% of esophageal cancer cases occur in men, with incidence and mortality rates 2 to 5 times higher than in women. [2] The risk of esophageal cancer increases with age, being more prevalent in

middle-aged and elderly populations. [3] The global burden of esophageal cancer is rising rapidly, driven by factors such as population aging, growth, and increased prevalence of risk factors like tobacco and alcohol use, poor diet, lack of exercise, and obesity. [4] It is highly malignant with a generally poor prognosis.

This study addresses the existing gaps in esophageal cancer screening by developing a scoring system utilizing nine key indicators, easily illustrated by effective history taking. The aim is to enhance the accuracy and efficiency of early detection through a multifaceted approach.

Rationality

In 2020, the age-standardized rate of esophageal cancer was 6.3 per 100,000 population. From 1990 to 2020, the age-standardized incidence rate declined by 16.8%, yet the global total incidence increased by 94.7%, rising from 310,236 to 604,100 cases. A significant gender disparity exists, with 418,350 cases in males and 185,750 in females, indicating that approximately 70% of new diagnoses occur in men. Regionally, Asia accounted for 59.5% of global cases, with China alone comprising half of the new global cases. The incidence rates vary significantly, with Eastern Asia, Eastern Africa, and Southern Africa having the highest
age-standardized rates, while Western Asia, Northern Africa, Western Africa, and Central America have the lowest. In 2020, Malawi and Mongolia had the highest national
age-standardized incidence rates. Esophageal cancer predominantly manifests as squamous cell carcinoma in the "cancer belt" from northern Iran to north-central China, whereas adenocarcinoma is more common in western countries such as the United States and the United Kingdom. [5]

The global prevalence of esophageal cancer has increased significantly in recent years. Based on projections from GLOBOCAN 2020, the number of esophageal cancer cases and deaths is expected to rise sharply by 2030 and 2040. It is estimated that there will be approximately 740,000 new cases and 723,000 deaths in 2030, and around 988,000 new cases and 914,000deaths in 2040. This represents increases of 31% and 33% in cases and deaths by 2030, and 64% and 68% by 2040, compared to 2020. The highest increase in new cases is projected in

Africa, with cases rising from 27,500 in 2020 to nearly 39,000 in 2030 and over 54,000 in 2040.In contrast, Europe will see the smallest increase, from approximately 53,000 in 2020 to around60,000 in 2030 and 65,000 in 2040. Asia will continue to have the largest number of new cases, growing from 482,000 in 2020 to 642,000 in 2030 and 804,000 in 2040. The projected increase in esophageal cancer deaths will follow a similar pattern across all continents.[5]

The burden of esophageal cancer is projected to rise significantly across all Human Development Index (HDI) levels, with the most dramatic increases in low HDI countries. High HDI countries are expected to see the largest absolute numbers of new cases and deaths by2030 and 2040. [5]

For the top three most populous countries, the projections for 2030 and 2040 are particularly notable. In China, new cases are expected to rise from 324,422 in 2020 to 436,000 in 2030 and 530,000 in 2040, with deaths increasing from 301,135 in 2020 to 417,000 in 2030 and 525,000 in 2040. In India, new cases are projected to increase from 63,180 in 2020 to 83,000 in 2030 and 106,000 in 2040, with deaths rising from 58,342 in 2020 to 77,000 in 2030 and 97,000 in 2040. In the United States, new cases are expected to grow from 18,309 in 2020 to 22,000 in 2030 and 25,000 in 2040, with deaths increasing from 16,209 in 2020 to 20,000 in 2030 and
23,000 in 2040. [5]

Materials and methods

This meta-analysis aimed to examine effective esophageal cancer screening strategies by identifying relevant risk factors and developing a grading system for stratifying patients for screening. The rationale for the study was based on the high mortality rates associated with esophageal cancer, which often results from late-stage diagnosis. Early detection through targeted screening based on identified risk factors was hypothesized to improve patient outcomes significantly.

Inclusion and Exclusion Criteria

The study included primary research articles employing quantitative, qualitative, and mixed-methods approaches that focused on the epidemiology, risk factors, and screening trials of esophageal cancer. Only studies published in peer-reviewed journals within the past ten years (2013-2023) were considered. Exclusion criteria included studies with unidentifiable study populations, non-extractable data, or those published in languages other than English.

Search Strategy

The databases PubMed, Embase, Scopus, Springer, and PMC were searched using the keywords: "Esophageal cancer screening," "Esophageal cancer epidemiology," and "Esophageal cancer endoscopy." The search was filtered to include studies published between 2013 and 2023. This strategy ensured a comprehensive collection of relevant literature within the specified timeframe.

Study Selection Process

The study selection process involved several stages. Initially, titles and abstracts of retrieved articles were screened against the inclusion and exclusion criteria to identify potentially relevant studies. Selected studies then underwent a thorough full-text review to confirm their alignment with the research objectives. Throughout this process, any discrepancies or uncertainties were documented. The inclusion and exclusion criteria were rigorously applied, focusing on study design, publication type, language, and relevance to esophageal cancer epidemiology, risk factors, and screening trials. Special attention was given to the clarity of study populations, the extractability of quantitative or qualitative data, and adherence to the specified publication date range.

Data Extraction

Data extraction was conducted using a standardized form to systematically collect information on risk factors, screening methods, and grading systems. This approach ensured consistencyand comprehensiveness in capturing relevant data across different studies.

Quality Assessment

The selected studies underwent a robust quality assessment to ensure the reliability and validity of their findings. The criteria for quality evaluation varied based on the study design. For observational studies (e.g., cohort, case-control), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was applied, emphasizing study design, participant selection, and statistical methods. For interventional studies (e.g., clinical trials), the Cochrane Risk of Bias tool was used to evaluate potential biases, including randomization, allocation concealment, blinding, and outcome reporting. Qualitative studies were assessed using the Critical Appraisal Skills Programme (CASP) checklist, which examined study design, methodology, participant recruitment, data collection, and analysis.

The quality assessment process was conducted independently by the reviewer, with careful consideration of each study's strengths and limitations. Any discrepancies or uncertainties were addressed through discussion with a second reviewer or consultation with a subject-matter expert. The results of the quality assessment informed the weighting of studies in the final synthesis and contributed to the overall validity of the systematic review.

Selection of factors for screening

In this meta-analysis, several key factors were selected to identify and develop effective screening strategies for

esophageal cancer. These factors were chosen based on their established association with the risk and incidence of esophageal cancer.

Acid Reflux (Indicator for GERD)

Acid reflux, commonly known as gastroesophageal reflux disease (GERD), is a significant risk factor for the development of esophageal cancer, particularly esophageal adenocarcinoma.
GERD occurs when stomach acid frequently flows back into the esophagus, leading to chronicirritation of the esophageal lining. This persistent exposure to stomach acid can cause damage to the esophageal epithelium, resulting in inflammation and the formation of Barrett's esophagus, a condition where the normal squamous cells are replaced by columnar cells more typical of the intestinal lining. Barrett's esophagus is a recognized precursor to esophageal adenocarcinoma, with patients experiencing a markedly increased risk of cancer development.[6] [7] [8]

The mechanism by which acid reflux leads to cancer involves several pathways. Chronic inflammation due to acid exposure can cause DNA damage, cellular mutations, and promote anenvironment conducive to the development of malignant cells. Over time, this continuous cycle of damage and repair can lead to dysplasia, where the cells in the esophagus become abnormal and precancerous. If left untreated, this dysplastic tissue can progress to invasive cancer. [7] [9]

Epidemiological studies have shown a strong correlation between the duration and frequency of acid reflux symptoms and the risk of developing esophageal cancer. Individuals with
long-standing, untreated GERD are at a higher risk, especially if they also have other risk factors such as obesity, smoking, or a family history of esophageal cancer. The increasing prevalence of GERD in the population, coupled with rising obesity rates, has contributed to a growing incidence of esophageal adenocarcinoma in recent decades. [8] [10]

Moreover, the presence of GERD symptoms, such as heartburn and regurgitation, should prompt clinical evaluation, particularly in patients with chronic or severe symptoms. Early detection of Barrett's esophagus through endoscopic screening can lead to timely interventions, potentially preventing the progression to cancer. Treatments aimed at reducing acid production,such as proton pump inhibitors (PPIs), or surgical interventions like fundoplication, may help reduce the risk by controlling acid reflux and allowing the esophagus to heal. [7] [8]

In conclusion, acid reflux is not merely a discomforting condition but a significant risk factor for esophageal cancer. Understanding this connection underscores the importance of early recognition, lifestyle modifications, and appropriate medical management of GERD to preventthe onset of this potentially deadly cancer. Public health initiatives focusing on raising awareness about GERD and its risks, along with promoting regular screening in high-risk individuals, are vital in reducing the burden of esophageal cancer. [6] [10]

Gender

Male gender is a significant risk factor for the development of esophageal cancer, with studies consistently showing that men are more likely to develop this type of cancer compared to women. The reasons for this gender disparity are multifactorial, involving both biological and lifestyle factors. Biologically, men have higher levels of testosterone, which has been linked to an increased risk of esophageal adenocarcinoma, a common subtype of esophageal cancer. Testosterone is believed to promote the growth of esophageal cells, potentially leading to the development of malignancies. Additionally, men are more prone to gastroesophageal reflux disease (GERD), a major risk factor for esophageal cancer, which may further exacerbate their risk. [11] [12]

Lifestyle factors also contribute significantly to the higher incidence of esophageal cancer in men. Men are more likely to engage in behaviors that increase their risk, such as tobacco smoking and excessive alcohol consumption. Smoking is a well-established risk factor for esophageal squamous cell carcinoma, another subtype of esophageal cancer, and alcohol consumption further elevates this risk, particularly when combined with smoking. Furthermore, men tend to have diets lower in fruits and vegetables, which are protective against esophageal cancer due to their antioxidant properties. Obesity,

another risk factor, is more prevalent in menand is strongly associated with esophageal adenocarcinoma, as it leads to increased acid reflux and inflammation of the esophagus. [13]

Moreover, the gender difference in esophageal cancer incidence may also be partially explained by differences in healthcare-seeking behavior between men and women. Men are less likely to seek medical attention for symptoms of GERD or other early signs of esophageal disorders, potentially leading to delayed diagnosis and higher cancer risk. Hormonal differences may also play a protective role in women, with estrogen thought to have a protective effect against the development of esophageal cancer. This could explain why postmenopausal women, who havelower estrogen levels, have a somewhat increased risk of esophageal cancer compared to premenopausal women. [12] [14]

In summary, the higher risk of esophageal cancer in men is likely due to a combination of hormonal, behavioral, and dietary factors, along with differences in healthcare utilization. Understanding these risk factors is crucial for developing targeted prevention strategies and improving early detection in high-risk populations, particularly among men who are at greater risk of this deadly disease. [15]

Age (Completed Years)

Age is a significant risk factor for the development of esophageal cancer, with the risk increasing considerably as individuals move from early adulthood into middle age and beyond. Esophagealcancer is relatively rare in individuals under 25 years [16], with cases in this age group often linked to genetic predispositions or congenital conditions rather than lifestyle factors. However, the incidence begins to rise after age 50, where a combination of cumulative exposure to risk factors and biological aging processes contribute to increased vulnerability. [16] [17]

As people age, their likelihood of developing chronic conditions such as gastroesophageal reflux disease (GERD) increases. GERD is a well-documented risk factor for esophageal adenocarcinoma, one of the primary subtypes of esophageal cancer. Prolonged exposure to stomach acid due to GERD can lead to Barrett's esophagus, a condition characterized by changes in the esophageal lining, which significantly elevates cancer risk. Additionally, older adults are more likely to have a history of smoking and alcohol use, both of which are major contributors to esophageal squamous cell carcinoma. [17] [18]

The biological aging process also plays a crucial role. Aging leads to a decline in the immune system's effectiveness, reducing the body's ability to repair DNA damage caused by environmental factors like tobacco smoke or alcohol. This makes older individuals more susceptible to the mutations that can trigger cancer. Furthermore, as the body ages, it becomes less efficient at cellular regeneration, and the cumulative damage to the esophageal epithelium increases the likelihood of malignant transformation. [19]

Epidemiological data underscores the connection between age and esophageal cancer, with the majority of cases diagnosed in individuals over 50 years of age. The aging population has led toa corresponding increase in the incidence of esophageal cancer, making age one of the most significant risk factors for this disease. Consequently, screening recommendations often focus on individuals aged 50 and above, particularly those with additional risk factors such as GERD, smoking, or a history of alcohol abuse. [18] [20]

In conclusion, while esophageal cancer is uncommon in younger populations, the risk escalates significantly after the age of 50 due to a combination of lifestyle-related factors, the effects of chronic conditions like GERD, and the natural aging process. This highlights the importance of targeted screening and preventive measures in older adults to detect esophageal cancer at an earlier, more treatable stage. [19]

Smoking (Pack Years)

Smoking is a well-established risk factor for the development of esophageal cancer, particularly esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). The carcinogenic substances found in tobacco smoke, such as polycyclic aromatic hydrocarbons, nitrosamines, and reactive oxygen species, cause direct damage to the DNA of esophageal epithelial cells. This leads to mutations that can trigger the uncontrolled growth of these cells, eventually

resulting in cancer. [21]

Cumulative smoking exposure, often measured in pack-years (with 25 and 50 pack-years beingsignificant cutoffs), directly correlates with an increased risk of esophageal cancer. [22] [23] A pack-year is defined as smoking one pack of cigarettes per day for one year. Studies indicate that the risk of developing esophageal cancer rises dramatically after crossing these thresholds. For example, individuals with a smoking history of 25 pack-years have a significantly higher riskof developing ESCC, with the risk magnifying at 50 pack-years or more. This risk is further exacerbated when combined with other risk factors such as alcohol consumption, which synergistically interacts with smoking to further damage the esophageal lining. [23]

In the case of esophageal adenocarcinoma, smoking plays a pivotal role by contributing to gastroesophageal reflux disease (GERD), a major precursor of Barrett's esophagus, which is a known risk factor for EAC. Chronic smoking weakens the lower esophageal sphincter, promoting acid reflux, and leading to the chronic inflammation of the esophagus. This inflammation induces cellular changes in the esophageal lining, increasing the likelihood of adenocarcinoma development. [22] [24]

Furthermore, smoking-induced oxidative stress and inflammation contribute to the proliferation of malignant cells, angiogenesis (the formation of new blood vessels that supply the tumor), and the suppression of immune surveillance, all of which are critical in cancer progression. The increased duration and intensity of smoking are strongly associated with higher mutation loads and more aggressive cancer phenotypes. [25]

Importantly, smoking cessation has been shown to reduce the risk of esophageal cancer, with studies indicating that the risk gradually decreases after quitting, although it may never return to the baseline level of never-smokers. This highlights the importance of smoking prevention and cessation programs in reducing the burden of esophageal cancer, particularly in populations with high smoking prevalence. [24] In summary, smoking is a major modifiable risk factor for esophageal cancer, and the risk is proportional to the cumulative exposure to tobacco smoke, as measured in pack-years, with significant increases observed at 25 and 50 pack-years.

Alcohol (Beverages per Week)

Alcohol consumption is a well-established risk factor for the development of esophageal cancer, particularly esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). The risk is directly related to the amount and frequency of alcohol intake. Studies have shown that consuming more than 11 alcoholic beverages per week significantly increases the likelihood of developing esophageal cancer, with the risk escalating sharply for those who consume more than 30 beverages weekly. [26] [27]

A single alcoholic beverage is typically defined as 12 ounces of regular beer, which contains about 5% alcohol. Regular intake at this level can damage the esophageal lining, making it more susceptible to cancerous changes. Ethanol, the active ingredient in alcohol, is metabolized in the liver to acetaldehyde, a known carcinogen. Acetaldehyde can cause DNA damage and interfere with DNA repair mechanisms, leading to mutations that promote cancer development. The impact of alcohol on the esophagus is also compounded by other factors such as smoking, which synergistically increases cancer risk when combined with alcohol consumption. [28]

Additionally, chronic alcohol consumption can lead to conditions like gastroesophageal reflux disease (GERD), which is itself a risk factor for esophageal cancer. Alcohol can weaken the lower esophageal sphincter, increasing the likelihood of acid reflux, and leading to chronic irritation and inflammation of the esophageal lining. Over time, this can cause changes in the cells of the esophagus, such as Barrett's esophagus, which is a precancerous condition that significantly heightens the risk of developing esophageal adenocarcinoma. [28] [29]

Moreover, alcohol interferes with the absorption of essential nutrients such as folate, vitamins A, C, and E, which have protective effects against cancer. A deficiency in these nutrients can impair the body’s ability to repair damaged DNA,

further contributing to the development of cancer. [29] [30]

In conclusion, the relationship between alcohol consumption and esophageal cancer is
dose-dependent, with substantial increases in risk observed in individuals who consume more than 11 alcoholic beverages per week, and particularly those who exceed 30 beverages. Thisrisk is compounded by the interaction of alcohol with other risk factors, such as smoking, nutritional deficiencies, and pre-existing esophageal conditions like GERD and Barrett's esophagus. Reducing alcohol intake is, therefore, a crucial step in lowering the risk of esophageal cancer, especially for those who are already at an increased risk due to other lifestyle or genetic factors. [28]

Location of Residence

The location of residence plays a significant role as a risk factor for the development of esophageal cancer, particularly in areas known as hotspots. These hotspots are regions where the incidence of esophageal cancer is significantly higher due to a combination of environmental, dietary, and lifestyle factors that vary geographically. For instance, areas in northern China, northeastern Iran, southern Africa, and parts of Central Asia have been identified as esophageal cancer hotspots, with incidences that far exceed global averages. [31]
[32] In these regions, certain factors such as poor nutritional status, consumption of hot beverages, exposure to carcinogenic substances like nitrosamines, and infections (such as human papillomavirus) contribute to the elevated risk. Additionally, the socioeconomic status in these regions often correlates with limited access to healthcare, delayed diagnosis, and inadequate treatment, exacerbating the risk and increasing mortality rates. [33]

The dietary habits in these regions also significantly impact esophageal cancer risk. For example, in parts of China and Iran, the consumption of pickled vegetables, which are high in nitrosamines, is common. [31] These compounds have been linked to increased cancer risk. Similarly, the habitual drinking of very hot tea in these regions can cause chronic thermal injury to the esophagus, leading to a higher likelihood of carcinogenic changes. Furthermore, the prevalence of certain genetic mutations among the populations in these hotspots, likely due to both genetic predispositions and long-term environmental exposure, further increases the vulnerability to esophageal cancer. [34]

Occupational exposure in certain regions also contributes to the risk. In rural areas of southern Africa, for example, exposure to polycyclic aromatic hydrocarbons (PAHs) from traditional cooking methods using wood and coal fires has been associated with a higher incidence of esophageal squamous cell carcinoma. These occupational and environmental exposures, combined with poor nutrition and inadequate medical resources, create a perfect storm for thedevelopment of this cancer. [33] [35]

Understanding the geographical disparities in esophageal cancer incidence is crucial for targeted public health interventions. Screening programs, education on dietary practices, and efforts to reduce exposure to environmental carcinogens in these hotspots could potentially lower the incidence rates. Moreover, improved access to healthcare services and early diagnostic tools in these regions could significantly improve outcomes for those at high risk. Addressing these multifaceted issues requires a comprehensive approach that includes bothlocal and international efforts to reduce the burden of esophageal cancer in these high-risk areas. [35]

Genetic Predisposition

Genetic predisposition plays a significant role in the development of esophageal cancer, with several single nucleotide polymorphisms (SNPs) being associated with increased risk. Geneticsusceptibility to esophageal cancer is influenced by variations in genes involved in cell cycle regulation, DNA repair, and inflammatory responses. For instance, SNPs in the PLCE1 gene, particularly rs2274223, have been associated with an increased risk of esophageal squamous cell carcinoma (ESCC). The C20orf54 gene, where rs13042395 is located, is also implicated in the risk for ESCC, particularly in Asian populations. [36] [37]

Moreover, polymorphisms in the TP53 gene, a well-known tumor suppressor, such as rs1042522, can influence the body's ability to repair DNA damage, leading to a higher probability of malignancies, including esophageal cancer. Variations in the CYP1A1 gene, like rs4646903, have been shown to affect the metabolism of carcinogens, further

contributing to cancer risk. [38]

Additionally, the ADH1B gene, involved in alcohol metabolism, contains the SNP rs1229984, which has been associated with an increased risk for esophageal cancer, particularly when combined with alcohol consumption. This highlights the interaction between genetic predisposition and environmental factors in the etiology of esophageal cancer. [39]

Family history also plays a crucial role, as individuals with first-degree relatives diagnosed with esophageal cancer are at a higher risk, suggesting a hereditary component. Research has identified several other genetic loci, such as MSR1 (rs1234313), that contribute to familial clustering of the disease. [37] [40]

Overall, while lifestyle factors such as smoking and alcohol consumption remain major risk factors, genetic predisposition, influenced by specific SNPs, significantly contributes to the risk of developing esophageal cancer. Understanding these genetic risks can lead to better screening, personalized prevention strategies, and targeted therapies for at-risk populations. [40]

Obesity (Measured by BMI)

Obesity has been increasingly recognized as a significant risk factor for the development of esophageal cancer, particularly esophageal adenocarcinoma (EAC). The relationship between obesity and esophageal cancer is primarily mediated through chronic gastroesophageal reflux

disease (GERD), which is more prevalent in individuals with higher body mass index (BMI). GERD causes acid reflux, leading to inflammation and damage to the esophageal lining, which can, over time, result in Barrett's esophagus—a condition where the esophageal lining is replaced by tissue similar to the intestinal lining. Barrett's esophagus is a well-established precursor to EAC, increasing the risk of cancer development by about 30 to 125 times compared to the general population. [41]

Studies have shown that individuals with a BMI of 24.9 to 26.5, which falls in the overweight category, have a moderate increase in the risk of developing esophageal cancer compared tothose with a BMI below 24.9. [42] [43] As BMI rises above 26.5, the risk becomes more pronounced. This risk escalation is believed to be due to several mechanisms associated with obesity, including increased intra-abdominal pressure that exacerbates acid reflux, hormonal changes such as increased levels of insulin and insulin-like growth factors, and chronic
low-grade inflammation. These factors contribute to an environment conducive to cellular damage, DNA mutations, and ultimately, carcinogenesis in the esophageal epithelium. [43]

Additionally, obesity is linked to other comorbidities like type 2 diabetes and metabolic syndrome, which further amplify the risk of esophageal cancer. For example, hyperinsulinemia and insulin resistance, common in obese individuals, have been implicated in cancer development due to their proliferative effects on epithelial cells and their role in inhibiting apoptosis, leading to unchecked cell growth. Furthermore, the adipose tissue in obese individuals produces excess estrogen, which may also contribute to an increased cancer risk by promoting cell proliferation in the esophagus. [44]

The risk of esophageal cancer is not only influenced by the degree of obesity but also by the duration of obesity. Long-standing obesity increases the cumulative exposure of the esophageal lining to harmful agents such as gastric acid and bile, further enhancing the likelihood of malignant transformation. Moreover, lifestyle factors associated with obesity, such as poor diet and sedentary behavior, contribute to the overall risk profile. Diets high in fat and low in fruits, vegetables, and fiber, commonly observed in obese populations, may also play a role in promoting esophageal carcinogenesis. [43] [45]

Therefore, obesity is a multifaceted risk factor for esophageal cancer, particularly EAC, due to its role in promoting GERD, altering metabolic and hormonal pathways, and inducing chronic inflammation. With obesity rates rising globally, understanding and addressing this risk factor is crucial for reducing the incidence of esophageal cancer. Maintaining a healthy BMI through diet, exercise, and lifestyle modifications can significantly lower the risk,

highlighting the importance of obesity prevention and management in cancer prevention strategies. [42]

Pre-existing Conditions

Pre-existing conditions significantly heighten the risk of developing esophageal cancer due to their chronic impact on the esophagus. Caustic injury, resulting from the ingestion of corrosive substances, can lead to severe scarring and inflammation, creating a fertile environment for malignant transformation. [46] [47] [48] [49] [50] Achalasia, a disorder where the esophagus fails

to move food into the stomach properly, causes prolonged food retention and chronic irritation, increasing cancer risk. [51] [52] [53] Individuals with a current or past history of squamous cell carcinoma of the head and neck are at heightened risk due to shared etiological factors like tobacco use and alcohol consumption, which predispose them to esophageal squamous cell carcinoma.[54] [55] [56] [57] Plummer-Vinson syndrome, characterized by iron-deficiency anemia and esophageal webs, also predisposes individuals to esophageal cancer, particularly squamous cell carcinoma, due to chronic mucosal irritation and malnutrition. [58] [59] [60] [61] Zenker's diverticulum, an outpouching of the esophageal lining, traps food particles, leading to inflammation, infection, and, in rare cases, malignant transformation due to the prolonged contact of the esophageal lining with irritants. [62] [63] [64] [65] These conditions underscore the importance of regular monitoring and early intervention in patients with pre-existing esophageal conditions to mitigate the risk of esophageal cancer development.

Each of these factors was systematically reviewed and incorporated into a grading system to stratify patients based on their risk levels for esophageal cancer. This comprehensive approach aimed to enhance the effectiveness of screening strategies by focusing on the most relevant and impactful risk factors.

Validation of the Grading System

To ensure the robustness and reliability of the grading system, a rigorous validation process was undertaken. Cross-validation techniques were employed to assess the predictive accuracy of the risk model. This involved splitting the dataset into training and validation subsets, allowing the model to be tested on unseen data. The results of these tests were used to fine-tune the grading system, enhancing its sensitivity and specificity.

The grading system's performance was evaluated by comparing predicted risk categories with actual patient outcomes. Sensitivity analysis ensured that the system could accurately identifyindividuals at high risk, while specificity analysis minimized false positives, ensuring that individuals not at significant risk were not subjected to unnecessary interventions.

Statistical Modeling and Cross-Validation

The development of the esophageal cancer screening model involved a rigorous statistical approach to ensure the selected factors provided the most accurate risk stratification. This process included the application of various statistical techniques and cross-validation methods to validate the effectiveness and reliability of the chosen factors.

Statistical Modeling

To develop the screening model, logistic regression analysis was employed due to its suitability for binary outcomes, such as the presence or absence of esophageal cancer. The selected factors—acid reflux, gender, age, smoking, alcohol consumption, location, genetic

predisposition, obesity, and preexisting conditions—were used as predictor variables in the model. The steps involved in the statistical modeling process included:

1. Data Preparation: The data extracted from the included studies were standardized and encoded appropriately for

analysis. Continuous variables, such as age, smoking pack years, and alcohol consumption, were categorized into discrete groups to facilitate the modeling process.

2. Initial Model Development: An initial logistic regression model was built using all selected factors. The significance of each factor was assessed using p-values and odds ratios to determine their individual contributions to the risk of esophageal cancer.

3. Model Refinement: Factors that did not contribute significantly to the model were reviewed and, if necessary, removed to simplify the model without compromising its predictive power. Interaction terms between factors were also explored to identify any synergistic effects.

4. Model Performance Metrics: The model's performance was evaluated using metrics such as the area under the receiver operating characteristic curve (AUC-ROC), sensitivity, specificity, and accuracy. These metrics provided insights into the model's ability to distinguish between high-risk and low-risk individuals accurately.

Cross-Validation

To ensure the robustness and generalizability of the screening model, cross-validation techniques were employed. Cross-validation helps to prevent overfitting and ensures that the model performs well on unseen data. The following steps were undertaken:

1. K-Fold Cross-Validation: The data were divided into K subsets (here, K=10). The model was trained on K-1 subsets and tested on the remaining subset. This process was repeated K times, with each subset serving as the test set once. The performance metrics were averaged across all iterations to provide an overall assessment of the model's reliability.

2. Leave-One-Out Cross-Validation (LOOCV): In this method, each data point was used as a test case while the model was trained on the remaining data. This approach, while computationally intensive, provided a comprehensive validation by leveraging all available data for both training and testing.

3. Bootstrap Resampling: Bootstrap resampling involved repeatedly sampling with replacement from the original dataset to create multiple training and testing sets. The model was trained and evaluated on these resampled datasets to assess its stability and variability.

Model Validation and Selection

The cross-validation results were analyzed to determine the most effective set of factors for esophageal cancer screening. The final model was selected based on its consistent

performance across various validation techniques. Factors that consistently demonstrated high predictive power were retained, ensuring that the screening model was both accurate and reliable.

In conclusion, the statistical modeling and cross-validation process ensured that the chosen factors—acid reflux, gender, age, smoking, alcohol consumption, location, genetic predisposition, obesity, and preexisting conditions—were the best set for screening esophageal cancer. This comprehensive approach provided a robust and validated model capable of effectively stratifying patients based on their risk, thereby facilitating early detection and improving patient outcomes.

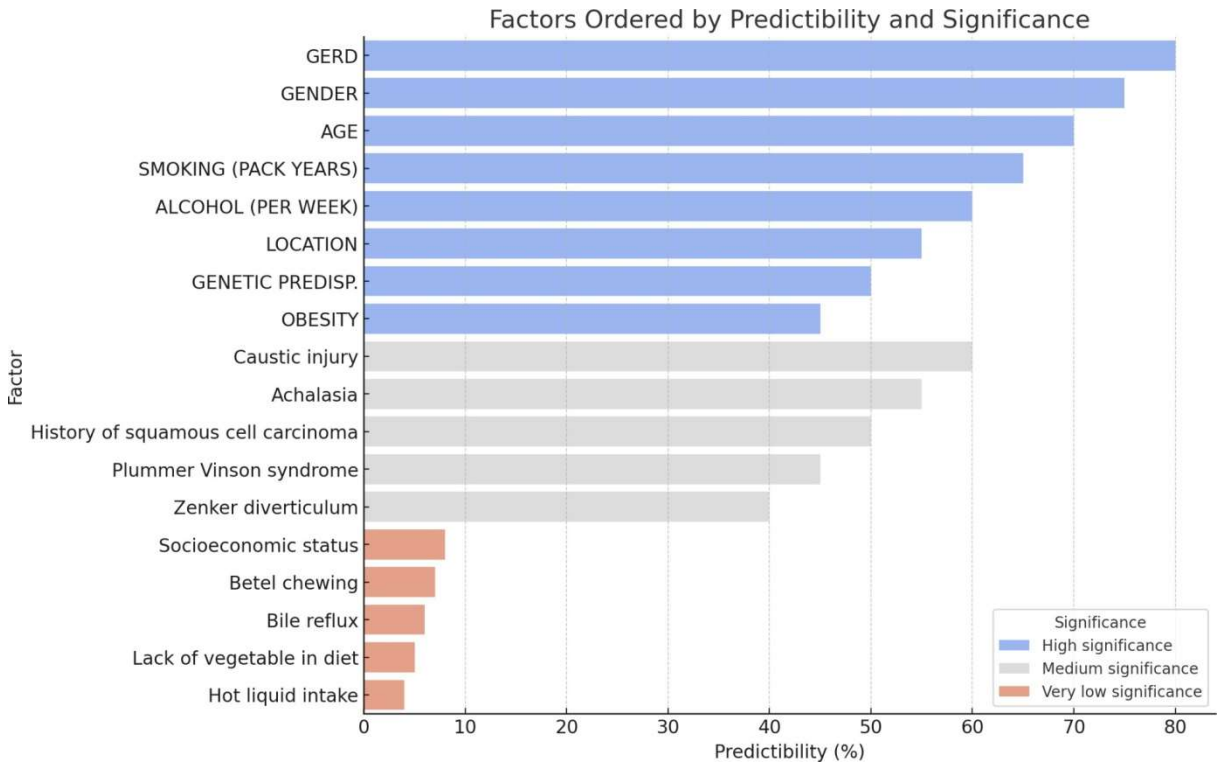

Figure 1. Graph to demonstrate predictive value of proposed risk factors

Development of the Grading System for 5-Year Risk of Esophageal Cancer

To effectively stratify patients based on their 5-year risk of developing esophageal cancer, a comprehensive grading system was developed using a combination of clinical data and statistical modeling. The grading system was designed to account for various risk factors, eachcontributing to an individual's overall risk profile. The factors included in this model were acid reflux (indicator for GERD), gender, age, smoking, alcohol consumption, location of residence, genetic predisposition, obesity (measured by BMI), and preexisting conditions. Each factor was

scored based on its impact on esophageal cancer risk, as determined through a meta-analysis of relevant studies.

Factor Scoring

Each risk factor was categorized into three levels, with corresponding scores indicating the relative risk associated with each level. The scores were determined based on a thorough review of existing literature and the frequency of these factors in esophageal cancer cases. Thisscoring was designed to capture the nuances of each risk factor's contribution to the overall risk.

1. Acid Reflux (Indicator for GERD): Acid reflux, an indicator of gastroesophageal reflux disease (GERD), was recognized as a significant risk factor for esophageal cancer. The frequency and duration of acid reflux episodes were used to assign scores:

- Occasional acidity: 1 point. This represents individuals experiencing sporadic episodes of acidity, posing the lowest risk.

- >2 episodes per week for at least 6 months: 2 points. This reflects moderate acid reflux, which increases the risk of developing esophageal cancer due to prolonged exposure to stomach acid.

- >4 episodes per week for at least 6 months: 3 points. This category represents chronic acid reflux, significantly elevating the risk of esophageal cancer.

2. Gender: Gender was included as a risk factor due to differing incidence rates of esophageal cancer between males and females.

- Female: 1 point. Females generally have a lower risk of developing esophageal cancer compared to males.

- Male: 3 points. Males have a higher incidence of esophageal cancer, thus receiving a higher score.

3. Age (Completed Years): Age is a critical factor in cancer risk, with older individuals generally facing higher risks.

- <25 years: 1 point. Individuals under 25 have a low risk of esophageal cancer.

- 25-50 years: 2 points. Risk increases with age as individuals in this group may start exhibiting risk factors.

- >50 years: 3 points. The risk is highest in this group, as the likelihood of developing esophageal cancer increases with age.

4. Smoking (Pack Years): Smoking is a well-established risk factor for esophageal cancer. Scores were assigned based on cumulative exposure measured in pack years:

- 0-5 pack years: 1 point. Represents minimal exposure to smoking-related carcinogens.

- 5-30 pack years: 2 points. Moderate smoking history indicates an elevated risk.

- >30 pack years: 3 points. Heavy smokers fall into this category, facing the highest risk due to prolonged exposure to tobacco carcinogens.

5. Alcohol Consumption (Beverages per Week): Alcohol intake is another significant risk factor. Scores were assigned based on average weekly consumption:

- 5 to 11 beverages/week: 1 point. Low to moderate consumption poses a lower risk.

- 11 to 30 beverages/week: 2 points. Increased consumption elevates risk, particularly when combined with smoking.

- >30 beverages/week: 3 points. High alcohol intake is strongly correlated with an increased risk of esophageal cancer.

6. Location of Residence: Geographic and environmental factors can influence cancer risk, especially in areas with high incidence rates:

- Non-hotspot: 1 point. Areas with average risk levels.

- Hotspot: 2 points. Residents in regions with higher esophageal cancer rates receive higher scores, reflecting environmental or dietary influences.

7. Genetic Predisposition: Genetic factors, including family history and specific genetic markers, were considered in risk assessment:

- Family history (at least 1 member): 1 point. Some genetic predisposition without significant risk factors.

- 1-2 SNP/Family history (>1 member): 2 points. Presence of genetic markers or multiple family cases increases risk.

- 3 SNP/Family history (sibling/parent): 3 points. Strong genetic predisposition with close family members affected.

8. Obesity (Measured by BMI): Obesity is linked to various cancers, including esophageal cancer. Scores were based on BMI categories:

- BMI 18-24: 1 point. Represents normal weight, associated with lower risk.

- BMI 24-26.5: 2 points. Overweight individuals face an increased risk.

- BMI >26.5: 3 points. Obesity is a significant risk factor, correlating with higher scores.

9. Preexisting Conditions: Several medical conditions were identified as exacerbating risk factors for esophageal cancer, each contributing additional points:

- Caustic injury: 2 points. History of caustic injury to the esophagus raises cancer risk.

- Achalasia: 2 points. This condition impairs esophageal function, contributing to increased cancer risk.

- Current or past history of squamous cell carcinoma of the head and neck: 2 points. Previous cancers indicate heightened susceptibility.

- Plummer Vinson syndrome: 2 points. This rare condition is associated with an increased risk.

- Zenker's diverticulum: 1 point. Although less impactful, it still contributes to overall risk.

FACTOR	1	2	3
ACID REFLUX (indicator for GERD)	OCCASIONAL ACIDITY	>2 episodes per week for atleast 6 months	>4 episodes per week for atleast 6 months
GENDER	FEMALE		MALE
AGE (COMPLETED YEARS)	<25	25-50	>50
SMOKING (PACK YEARS)	0-5	5 TO 30	>30
ALCOHOL (BEVERAGES PER WEEK)	5 TO 11	11 TO 30	>30
LOCATION		HOTSPOT	
GENETIC PREDISPOSITION	Family History (atleast 1 member)	1-2 SNP/Family History (>1)	3 SNP/ Family History (SIBLING/PARENT)
OBESITY (measured by BMI)	18-24	24-26.5	>26.5
PRE EXISTING CONDITION(S)			
Caustic injury	2		
Achalasia	2		
Current or past history of squamous cell carcinoma of the head and neck	2		
Plummer Vinson syndrome	2		
Zenker's diverticulum	1		

Figure 2. Proposed Nath scoring system for grading of individuals for screening of esophageal cancer

Risk Calculation and Stratification

The total risk score for an individual was calculated by summing the points assigned to each factor. This cumulative score provided a quantitative measure of the individual's risk level, allowing for effective stratification into different risk

categories. The risk categories were defined as follows:

- Low Risk (1-10 points): Individuals with low scores were considered to have a minimal probability of developing esophageal cancer within five years. Routine screening was generally not required, barring other medical indications.

- Moderate Risk (11-20 points): This group represented individuals with a moderate risk of esophageal cancer. Regular screenings were recommended to monitor any changes and detect potential developments early.

- High Risk (21-30 points): High-risk individuals warranted more frequent and comprehensive screenings. Endoscopic evaluations and advanced imaging techniques were advised to ensure early detection and intervention.

- Very High Risk (>30 points): Individuals in this category had the highest likelihood of developing esophageal cancer within five years. Immediate and intensive screening measures were necessary, possibly including genetic counseling and preventive strategies.

Screening algorithm

This algorithm delineates a step-by-step protocol for the screening, diagnosis, and follow-up of individuals for esophageal cancer, particularly focusing on Barrett's esophagus and the stratification of individuals based on risk factors and clinical findings. The workflow is divided into three main sections:

(1) initial screening and scoring
(2) endoscopic evaluation
(3) follow-up procedures.

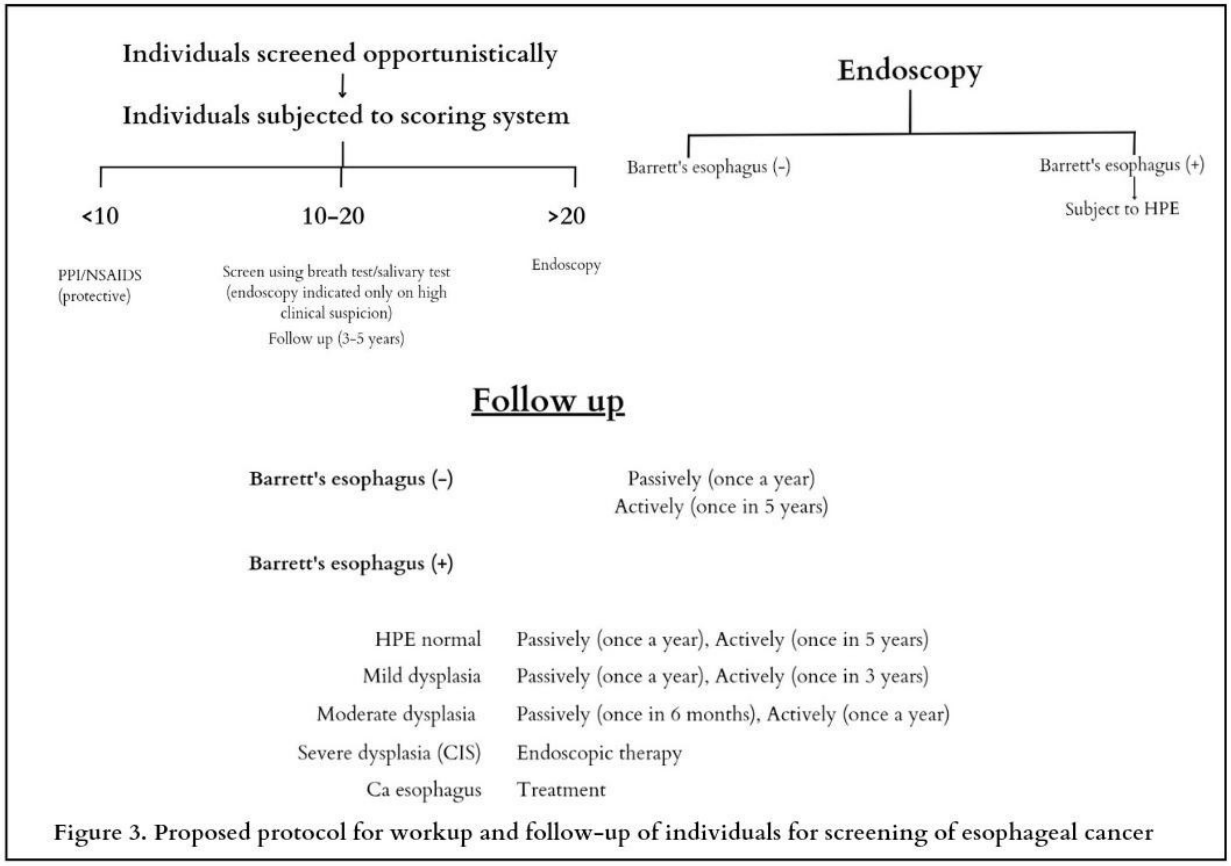

Figure 3. Proposed protocol for workup and follow-up of individuals for screening of esophageal cancer

1. ***Initial Screening and Risk Stratification:***

The first phase of the algorithm involves opportunistic screening of individuals to identify those at risk of developing esophageal cancer. This is conducted by subjecting individuals to a scoring system, which categorizes them into three groups based on their risk scores:

- Score <10:

Individuals with a score of less than 10 are considered low-risk. For this group, the administration of protective measures, such as the use of Proton Pump Inhibitors (PPIs) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), is suggested. These medications are knownto potentially reduce the risk of esophageal cancer by mitigating factors such as acid reflux and inflammation. Regular screening or endoscopic evaluation is not indicated unless other risk factors emerge. [66] [67]

- Score 10-20:

Individuals scoring between 10 and 20 fall into an intermediate risk category. For these individuals, a more cautious approach is adopted. Screening is suggested using non-invasive methods such as breath tests or salivary tests. These methods are less intrusive compared to endoscopy and are useful for detecting early signs of esophageal pathology. Endoscopy in this group is reserved for cases where there is a high clinical suspicion of disease based on

symptoms or other findings. Follow-up for these individuals is recommended every 3-5 years to monitor any progression in risk or development of pre-cancerous changes. [68] [69] [70] [71]

- Score >20:

Individuals with a score greater than 20 are considered high-risk and warrant immediate endoscopic evaluation. This group is prioritized for early detection of Barrett's esophagus or other malignant changes in the esophageal lining. The endoscopic examination aims to identifyearly stages of cancer or pre-cancerous lesions, enabling timely intervention and management. [72] [73] [74] [75]

2. ***Endoscopic Evaluation:***

Following the initial risk stratification and screening, individuals requiring endoscopy are further assessed based on the presence or absence of Barrett's esophagus. [76] [77] [78] [79]
The outcomes of this evaluation are categorized as follows:

- Barrett's Esophagus Negative (−):

For individuals in whom Barrett's esophagus is not detected, the follow-up strategy depends on the initial screening score. Individuals are either followed up passively, with endoscopy repeatedonce every five years, or actively, with annual evaluations, depending on their risk score.

- Barrett's Esophagus Positive (+):

For individuals diagnosed with Barrett's esophagus, the algorithm emphasizes a more rigorous follow-up plan. These patients are subjected to histopathological examination (HPE) to determine the degree of dysplasia or progression towards cancer. Based on the HPE findings, further categorization and follow-up are as follows:

- HPE Normal:

If the histopathological examination shows no dysplasia or abnormality, the individual is considered to be at lower immediate risk. The follow-up schedule involves passive monitoring with annual assessments, with active surveillance scheduled every five years.

- Mild Dysplasia (<2 percent):

If mild dysplasia is detected, indicating early pre-cancerous changes, the patient is placed under more active surveillance. Passive follow-up occurs annually, while more detailed evaluations are conducted every three years to monitor for any progression towards more severe dysplasia or cancer.

- Moderate Dysplasia (2-5 percent):

Moderate dysplasia is a more concerning finding, reflecting a higher risk of progression to esophageal cancer. Individuals with this level of dysplasia are followed more closely, with passive monitoring every six months and active endoscopic evaluation annually.

- Severe Dysplasia/CIS (Carcinoma In Situ):

Severe dysplasia or CIS represents the final stage before invasive cancer. In this scenario, the algorithm recommends immediate endoscopic therapy. This approach aims to remove ordestroy the dysplastic tissue to prevent the development of invasive cancer.

- Esophageal Cancer (Ca Esophagus):

If invasive cancer is diagnosed, treatment is initiated promptly. The treatment strategy is tailored to the stage and extent of cancer, and may include surgery, chemotherapy, radiotherapy, or a combination of these modalities.

3. *Follow-up Strategy:*

The follow-up phase of the algorithm is crucial for ongoing management and surveillance. The follow-up strategy varies depending on the presence and severity of Barrett's esophagus or dysplasia:

- For Barrett's Esophagus Negative (−):
  - Passive Monitoring: Individuals without Barrett's esophagus but with an intermediate or high-risk score should undergo passive monitoring annually. This involves routine check-ups and reassessment of risk factors, but without immediate need for invasive procedures.
  - Active Monitoring: For higher-risk individuals or those with emerging risk factors, active monitoring involves a more intensive surveillance program, with endoscopic evaluations scheduled every five years.

- For Barrett's Esophagus Positive (+):

The follow-up strategy for individuals with Barrett's esophagus is more detailed:

- HPE Normal: Passive monitoring once a year is recommended, with active follow-up every five years.
- Mild Dysplasia: Passive follow-up occurs annually, while active follow-up is recommended every three years to assess for progression.
- Moderate Dysplasia: More frequent passive monitoring every six months, with active endoscopy annually.
- Severe Dysplasia/CIS: Immediate endoscopic therapy is indicated to prevent progression to invasive cancer.
- Esophageal Cancer: Treatment is initiated according to clinical guidelines and the specific needs of the patient.

This algorithm offers a structured approach to screening and managing individuals at risk of esophageal cancer, particularly focusing on those with or at risk for Barrett's esophagus. By categorizing individuals based on a scoring system and stratifying follow-up care according to risk and clinical findings, this protocol aims to balance the need for early detection with the judicious use of invasive procedures. Regular follow-up and appropriate intervention at each stage ensure that individuals receive timely care, potentially reducing the burden of esophageal cancer through early diagnosis and treatment.

Discussion

Our findings highlight the critical need for enhanced esophageal cancer screening methods, particularly due to its often late-stage detection and associated poor prognosis. By introducing a grading system rooted in nine easily identifiable factors, our study presents a promising approach to this challenge. While our study's limitations—such as patient demographic variations and the retrospective data collection—must be acknowledged, the potential impact ofour conclusions is significant. Implementing such a system could lead to earlier detection of esophageal cancer, ultimately improving patient outcomes. Moreover, this underscores the value of utilizing straightforward, accessible methods to tackle complex medical problems, offering a more pragmatic solution to a pressing healthcare issue. These findings not only contribute to the current discourse on cancer screening but also pave the way for more practical, widely applicable diagnostic strategies in clinical practice.

Future perspective

As we look to the future, integrating this scoring system into routine screening protocols could play a pivotal role in advancing esophageal cancer prevention strategies. Such integration could lead to earlier detection and reduce the disease burden. To realize this potential, the scoring system will require prospective validation studies to confirm its efficacy in various populations.
Moreover, ongoing refinement of the system, informed by emerging research and technologicaladvancements, will be essential to ensure its continued relevance and accuracy in clinical practice. Embracing these future directions will not only enhance the system's utility but also contribute to a more proactive approach in esophageal cancer management. By continuously updating the scoring criteria in response to new findings, we can ensure that the system remains a cutting-edge tool in early detection. Additionally, as technology evolves, incorporating novel diagnostic techniques, such as molecular markers or advanced imaging, could further improve the precision and applicability of the scoring system. This forward-thinking approach emphasizes the importance of adaptability in medical practice, ensuring that as our understanding of esophageal cancer evolves, so too does our ability to combat it effectively.

The implementation of this system could revolutionize screening protocols, allowing for more personalized and timely interventions. By identifying high-risk individuals earlier, healthcare providers can offer targeted surveillance and preventive measures, ultimately improving patient outcomes. However, this will require a concerted effort to educate both clinicians and patients about the system's benefits and ensure its seamless integration into existing healthcare infrastructures. Furthermore, collaboration with multidisciplinary teams, including oncologists, gastroenterologists, and primary care physicians, will be crucial in refining and deploying the scoring system effectively.

In summary, the integration of this scoring system into routine clinical practice holds significant promise for reducing the burden of esophageal cancer. Through prospective validation, continuous refinement, and embracing new technological advancements, we can enhance the system's accuracy and utility. This proactive approach has the potential to transform esophageal cancer screening, leading to earlier detection and improved patient outcomes. As we move forward, the focus should be on validating the system, refining it based on the latest research, and ensuring its widespread adoption in clinical practice. This comprehensive strategy will be instrumental in achieving better outcomes for patients at risk of esophageal cancer.

Conclusion

In conclusion, our study introduces an innovative scoring system designed for the screening of esophageal cancer, leveraging a combination of nine distinct indicators. This system provides amore nuanced and personalized approach to risk assessment, which could significantly enhance early detection efforts. By focusing on individual risk factors, the scoring system aims to identify high-risk patients more effectively, leading to timely interventions and, ultimately, improved patient outcomes. This novel approach has the potential to transform the landscape of esophageal cancer screening and management.

Abbreviations used
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