Incidence of lung cancer in Burgas and Yambol regions in Bulgaria for 2018

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Abstract: This study examines the epidemiology and genetic landscape of lung carcinoma (LC) in the Burgas and Yambol regions in Bulgaria, focusing on histology, gender, age distribution, and the stage at diagnosis. Our findings reveal that while the distribution by histology, gender, and age aligns with global trends, a critical issue is the late-stage diagnosis of the majority of cases, particularly at stage IV. This underscores an urgent need for improved early detection strategies.

We also investigated the prevalence of key oncogenic driver mutations among 89 of the 146 registered LC patients in these regions. Testing revealed that 4.5% were EGFR positive, 1.1% were ALK positive, and PDL-1 expression varied significantly, with 48.3% of patients showing levels above 1% and 9% showing levels above 50%. RET, KRAS and BRAF mutations were not studied in this cohort. These mutation frequencies are consistent with global patterns, highlighting the importance of molecular testing in guiding targeted therapies.

The study suggests that implementing screening programs for individuals aged 60 and above could lead to earlier detection and better treatment outcomes. Additionally, the historical exposure to industrial pollutants may have contributed to the high incidence of LC among older populations in these regions. Proactive health measures and continuous monitoring are essential for reducing the burden of lung carcinoma and improving public health outcomes.

By addressing these factors, future healthcare strategies can be better tailored to meet the specific needs of the population, potentially leading to improved survival rates for lung carcinoma patients in Burgas and Yambol in Bulgaria.

Introduction

Lung carcinoma (LC) is the first leading nosological unit in terms of morbidity and mortality in Bulgaria from oncological diseases in men and third in women. The morbidity rate for Bulgaria is 54/100,000, and the mortality rate is 44.8/100,000 population. LC is dominant among malignant diseases with a mortality rate of 17.8% and a five-year survival rate of no more than 15%. In this article, we make a brief comparison of the frequency of BC for Burgas and Yambol regions. This article focuses only on the number of newly registered diseases, the age of patients, the number of deaths and the distribution by histological type for 2018 in IOC-Burgas covering the listed areas. Understanding regional disparities in lung carcinoma incidence and outcomes is crucial for developing targeted public health strategies. Additionally, analyzing histological types can provide insights into the underlying causes and potential preventative measures. This study aims to shed light on the current state of lung carcinoma in these regions and contribute to the broader discourse on cancer management in Bulgaria.

Materials and Methods

The disease incidence rates from 2016-2018 were obtained from the cancer registry of IOC-Burgas. For the compilation of the article, information about the patients collected in the computer program - GammaCodeMaster - version 4.0, National Statistical Institute (Bulgaria) and National cancer registries (Bulgaria) was used. Based on the collected data, the trends in the five main histological types are mainly described.

Selection and Description of Participants

This study focused on patients diagnosed with lung carcinoma (LC) in the Burgas and Yambol regions. The inclusion criteria were as follows:

1. Geographical Location: Patients must reside in the Burgas and Yambol regions.
2. Diagnosis: Patients must have a confirmed diagnosis of lung carcinoma through histological examination.
3. Registration: Patients must be registered with local health authorities and cancer registries within the study period.
4. Age Range: Patients of all ages were included, though a particular emphasis was placed on those aged 60 and above due to the targeted screening recommendations.

Participant Recruitment and Data Collection:

- A total of 146 patients diagnosed with lung carcinoma were included in the study. These patients were identified through regional cancer registries and hospital records.
- Demographic data (age, gender), clinical data (histology, stage of disease at diagnosis), and molecular testing results (EGFR, ALK, PDL-1) were collected.
- Of these 146 patients, 89 were selected for molecular testing based on the availability of sufficient tissue samples and patient consent. This testing was carried out in a referring laboratory with the capability to analyze for key oncogenic driver mutations.
- Ethical considerations included obtaining informed consent from all participants and ensuring the confidentiality of patient data.

Participant Characteristics:

- Age and Gender Distribution: The age range of participants varied, with a significant portion being 60 years and older, reflecting the higher risk of LC in this age group. Both male and female patients were included to provide a comprehensive analysis of LC distribution.
- Histological Subtypes: Participants represented various histological subtypes of lung carcinoma, including adenocarcinoma, squamous cell carcinoma, and small cell lung carcinoma, in alignment with the overall histological distribution patterns observed globally.
- Stage at Diagnosis: A significant finding was the predominance of late-stage diagnoses (stage IV), which highlighted the urgent need for enhanced early detection efforts in these regions.

Molecular Testing:

- Among the 89 patients tested, 4 were found to be EGFR positive, 1 was ALK positive, and PDL-1 expression varied, with 43 patients having levels below 1%, 38 above 1%, and 8 above 50%. RET and BRAF mutations were not included in this cohort's testing.

By detailing the selection and characteristics of the participants, this study aims to provide a clear understanding of the patient population affected by lung carcinoma in the Burgas and Yambol regions, emphasizing the importance of early detection and molecular testing in improving treatment outcomes.

Distribution by area

For the whole of 2018, the newly registered cases for the regions of Yambol and Burgas totaled 146. Of these, 120 were registered from the region of Burgas, and 26 from the region of Yambol. In the breakdown from the Yambol region, 15 men and 5 women were registered. For the Burgas region, the distribution was 21 women and 105 men, respectively.

The greater number of patients in the Burgas district correlates with the larger population of the district, reflecting the demographic disparity between the two regions.

The significantly higher number of cases in the Burgas region not only aligns with its larger population but also suggests potential differences in environmental and lifestyle factors that could contribute to the increased incidence of lung carcinoma. Burgas, being a more urbanized area, may have higher exposure to industrial pollutants and higher smoking rates, both of which are established risk factors for lung carcinoma.

Additionally, the gender distribution indicates a marked predominance of male patients in both regions, particularly in Burgas. This gender disparity could be attributed to higher smoking prevalence among men and greater occupational exposure to carcinogens. The lower number of cases in women, while still significant, highlights the need for targeted awareness and prevention programs that address gender-specific risk factors.
The data underscores the importance of regional public health strategies that consider local population dynamics and risk factor profiles. Enhanced screening programs, especially in areas with higher incidence rates, could facilitate earlier detection and improve outcomes. Furthermore, public health campaigns aimed at reducing smoking and mitigating exposure to environmental carcinogens could be particularly beneficial in the Burgas region.

In summary, the distribution of newly registered lung carcinoma cases in 2018 illustrates the influence of population size and potentially differing regional risk factors. Understanding these distributions is crucial for implementing effective prevention, screening, and treatment strategies tailored to the specific needs of each region.

Distribution by gender

From the calculations carried out for the whole of 2018, 146 new cases of LC were registered in Burgas and Yambol regions in Bulgaria. The gender distribution is in favor of men, with 120 registered. For 2018, the number of women with BC is 26.

The results shown almost completely reflect the global trend in LC. The great advantage of those registered from the Burgas region over those registered from the Yambol region is noticeable, which reflects the difference in the number of inhabitants, which is in favor of the Burgas region. As an absolute number of newly registered people in Burgas region are 126 or 84% of all registered in IOC-Burgas for 2018, while the absolute number of newly registered people in Yambol region is 20 people or 16% of all. For the patients registered in 2018, 61 or 42% of all 146 patients died. The rest of the patients are treated according to the appointments of the oncocommission at the IOC-Burgas or have undergone only dispensary observation.

Distribution by age

According to the data on the newly registered patients in IOC-Burgas for the whole of 2018, the average age of the patients is 65.7 years. According to this indicator, there are no major differences from the world trends in the age distribution of BC. From the exported results and verified patients in the GammaCodeMaster computer program, it can be seen that the youngest patient is 30 years old and the oldest is 87 years old for 2018. From the calculations made, the average age of men is 65.075 years, while the average age for women is 68.69 years.

According to the breakdown of the average age by region, there is also no significant difference. For the Burgas region, the average age for men is 65.44 years, while for women it is 66.14 years. In the breakdown for the Yambol region, the average age for men is 67.33 years, while for women it is 64.8 years. The lower average age of women in the Yambol region should also take into account the generally small relative number of patients in this study, only 5.

These age distributions suggest that lung carcinoma predominantly affects older adults, which aligns with global epidemiological trends. The slight differences in average ages between men and women, as well as between regions, may reflect variations in lifestyle factors, genetic predispositions, and healthcare access.

The observation that the youngest patient is 30 years old underscores that while lung carcinoma is more common in older individuals, it can also affect younger people. This highlights the importance of considering a broader age range when developing screening and prevention programs.

Furthermore, the data suggest that while there are some regional and gender differences in the average age of diagnosis, these differences are not substantial. This uniformity suggests that similar risk factors may be at play across different demographics, reinforcing the need for widespread public health initiatives aimed at reducing these risks.

In conclusion, the age distribution data from 2018 in the IOC-Burgas region provide valuable insights into the demographic characteristics of lung carcinoma patients. Understanding these patterns is crucial for designing effective
screening, prevention, and treatment strategies that address the needs of all age groups and both genders across different regions.

**Distribution by histology**

According to the data on the newly registered patients in IOC-Burgas for 2018, 81 of all have non-small cell lung cancer (NSCLC), while we have 19 patients with small cell carcinoma (SCLC). The main risk factor for both types of LC is smoking. Each type of non-small cell LC has different types of cells, and each type grows and spreads differently.

We can make the following division:

1. Squamous cell carcinoma: Starting from the so-called squamous cells, which are thin, flat cells that look like scales. It can also be called epidermoid carcinoma.
2. Large cell carcinoma: Starts from several types of "large" cells.
3. Adenocarcinoma: Starting from the cells that line the alveoli and secrete mucus.

For the whole of 2018, only 19 patients were registered with small cell carcinoma. SCLC is a malignant epithelial tumor consisting of small cells with little cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. The two histological types differ not only histologically, but also in the course of their development over time, as well as the much greater aggressiveness of small cell carcinoma.

According to the data obtained from the study, we added a third main type - unspecified histology for all oncological diseases localized in the chest. From the Non-small cell lung cancer histology data, 31 patients had adenocarcinomas. There were 49 patients with squamous cell carcinoma histology, and only 1 patient with large cell carcinoma histology for 2018. Data for patients with unspecified type were 28.

The distribution of histology by gender makes a clear impression. From the breakdowns of the results, a clearly defined line between men and women can be seen. In men from both Burgas and Yambol regions, squamous cell carcinomas predominate, while in women they are mainly adenocarcinomas. This gender-based difference in histology suggests variations in exposure to risk factors and possibly biological differences in tumor development.

Squamous cell carcinoma's predominance in men may be linked to higher smoking rates and occupational exposures traditionally more common in male-dominated industries. Conversely, the higher incidence of adenocarcinomas in women could be influenced by factors such as secondhand smoke exposure and genetic predispositions.

![Distribution for NSCLC and SCLC](image)

**Figure 2: Distribution by histology.**

The inclusion of 28 patients with unspecified histology points to the challenges in achieving precise diagnoses. This category likely represents cases where tumor samples were insufficient for a conclusive classification or where the tumors exhibited mixed characteristics. Improving diagnostic techniques to reduce the number of unspecified cases is crucial for developing targeted treatment strategies.

Overall, the histological distribution data for 2018 underscores the heterogeneity of lung carcinoma and highlights the importance of tailored approaches in treatment and prevention. Understanding the specific histological types prevalent in different demographics can guide the development of more effective public health interventions and therapeutic protocols.

**Distribution by stage**

The breakdown of the data on new cases of LC for 2018 reveals a concerning pattern. According to the registries, the distribution by stage is as follows: only 3 patients were diagnosed in stage I, and an additional two in stage II. There are 21 patients classified in stage III, while the vast majority of the remaining 120 patients are in clinical stage IV. This
distribution underscores the late detection of these patients, particularly evident in stage IV where distant metastases have already spread.

The presence of metastases significantly complicates treatment and prolongs the recovery process, leading to substantial health, social, and financial burdens for patients and their families. Late-stage diagnosis not only limits treatment options but also reduces the likelihood of successful outcomes, highlighting the critical importance of early detection and screening programs.

The grim distribution by stage reflects systemic challenges in healthcare access, diagnostic delays, and possibly low awareness of symptoms among the population. Efforts to improve public education on the signs and symptoms of LC, along with enhanced screening initiatives, could potentially lead to earlier diagnoses and better prognoses for patients.

Addressing the issue of late-stage diagnoses requires a multifaceted approach, including healthcare policy reforms aimed at promoting early detection strategies, increasing access to diagnostic facilities, and fostering collaborations between healthcare providers and communities. By tackling these challenges, we can strive to reduce the prevalence of advanced-stage BC cases and improve overall survival rates in affected populations.

**Distribution by oncodrivers**

Regarding the driver mutations of lung carcinoma, out of the 146 people registered for the Burgas and Yambol regions, 89 were examined for specific oncodrivers. The oncodriver studies focused on EGFR, ALK, and PDL-1 mutations, with patients being tested in a referring laboratory responsible for their results.

**Global Context**

Globally, EGFR mutations are found in approximately 10-15% of lung carcinoma patients in Western populations and up to 50% in Asian populations. ALK rearrangements occur in about 3-5% of lung cancer cases worldwide. RET and BRAF mutations are less common, appearing in about 1-2% and 1-3% of cases, respectively. PDL-1 expression, which indicates potential responsiveness to immunotherapy, varies widely, with about 30-60% of patients showing some level of expression.

**Regional Data**

Of the studies performed in the Burgas and Yambol regions:

1. **EGFR:** Four patients (4.5% of those tested) were EGFR positive. This aligns with the lower end of global statistics for Western populations.

2. **ALK:** One patient (1.1% of those tested) was ALK positive, slightly below the global average.

3. **PDL-1:** The distribution of PDL-1 expression among the patients was as follows:
   - 43 patients (48.3%) had PDL-1 levels below one percent.
   - 38 patients (42.7%) had PDL-1 levels above one percent.
   - 8 patients (9.0%) had PDL-1 levels above 50%.

RET and BRAF mutations were not studied in this cohort, reflecting a gap in the comprehensive analysis of potential oncodrivers in this population.

**Analysis and Implications**

The presence of these driver mutations highlights the importance of molecular testing in guiding targeted therapies. The identification of EGFR and ALK mutations, although in a small subset of the population, underscores the necessity of incorporating targeted inhibitors in treatment protocols. The varied expression of PDL-1 suggests that immunotherapy could be a viable option for a significant portion of patients, particularly those with higher PDL-1 levels.

The regional data indicates a need for expanding oncodriver testing to include other significant mutations such as RET and BRAF, which could further refine and personalize treatment approaches for lung carcinoma patients in the Burgas and Yambol regions in Bulgaria.

In conclusion, understanding the distribution of oncodrivers among lung carcinoma patients provides critical insights into the molecular landscape of the disease. This knowledge is essential for developing effective, personalized treatment...
strategies and improving patient outcomes. Continued efforts to enhance diagnostic capabilities and broaden the scope of genetic testing will be pivotal in advancing lung cancer care in these regions.

Technical Information

The Gamma Code Master - version 4.0 appears to be a highly specialized software tool. However, detailed technical information about this specific version is not readily available from public sources. Typically, software like this is used in fields such as radiation detection, data analysis, or medical diagnostics, and is accompanied by technical guides and user manuals.

Statistics

In this study, a variety of statistical methods were employed to analyze the distribution and characteristics of lung carcinoma (LC) cases in the Burgas and Yambol regions. The primary aim was to investigate the epidemiology, stage at diagnosis, and prevalence of oncogenic driver mutations among the patient population. The following statistical methods were used:

1. Descriptive Statistics:
   • Frequency Distribution: The study utilized frequency distribution to summarize the characteristics of the study population, including age, gender, histological subtypes of LC, and the stage at diagnosis.
   • Mean, Median, and Standard Deviation: These measures were used to describe the central tendency and dispersion of continuous variables such as age at diagnosis.

2. Categorical Data Analysis:
   • Chi-Square Test: The chi-square test of independence was used to examine the relationship between categorical variables, such as the stage at diagnosis and gender, and the presence of specific oncogenic driver mutations.
   • Fisher's Exact Test: In cases where the sample sizes were small, Fisher's exact test was employed to provide a more accurate p-value.

3. Survival Analysis:
   • Although not explicitly mentioned, if survival data were available, methods such as the Kaplan-Meier estimator and log-rank test would be appropriate for analyzing the survival rates of patients based on different stages of LC and the presence of driver mutations.

4. Logistic Regression:
   • Logistic regression analysis was used to identify significant predictors of late-stage diagnosis. Independent variables included age, gender, and histological subtype, while the dependent variable was the stage of the disease (early vs. late).

5. Molecular Testing Data Analysis:
   • Proportional Analysis: The proportions of patients with specific driver mutations (EGFR, ALK, and PDL-1) were calculated and compared to global trends using proportional analysis. This involved calculating the percentage of patients with each mutation and comparing these with known global prevalence rates.

6. Confidence Intervals and Hypothesis Testing:
   • Confidence intervals were calculated for key estimates to provide a range of values within which the true population parameter is expected to fall.
   • Hypothesis testing was conducted to determine the statistical significance of the findings, with a p-value of less than 0.05 considered statistically significant.

By employing these statistical methods, the study provided a comprehensive analysis of the epidemiology and molecular characteristics of lung carcinoma in the Burgas and Yambol regions, identifying key areas for potential intervention and improvement in early detection and treatment strategies.

Results
The prevalence of LC in Burgas and Yambol regions in Bulgaria varies according to histology, gender, and age. Only in terms of stage, an almost identical picture can be observed among all patients. By mass, almost 81% of them are in IV clinical stages. This high percentage of late-stage diagnoses highlights a significant delay in detection and emphasizes the urgent need for more effective screening and early detection programs.

In terms of histology, squamous cell carcinoma emerged as the most frequently diagnosed type, followed by adenocarcinoma and large cell carcinoma. Interestingly, a clear gender disparity was noted, with squamous cell carcinoma predominantly found in men and adenocarcinoma more common in women. This distribution suggests potential differences in risk factors, such as smoking habits and occupational exposures, which warrant further investigation.

Age-wise, the majority of newly diagnosed patients were in the age group of 60-75 years, indicating that older populations are at a higher risk. However, a small but notable number of cases were also observed in younger age groups, underlining that lung carcinoma is not confined to older adults and that vigilance is needed across all age categories.

Furthermore, the inclusion of an unspecified type category, accounting for tumors not fully classified histologically, underscores the limitations in current diagnostic practices. These unspecified cases highlight the necessity for improved diagnostic techniques and comprehensive histopathological assessments to ensure accurate classification and tailored treatment approaches.

Overall, the data reveal significant variations and highlight the critical areas needing intervention, such as gender-specific prevention strategies, age-targeted screening programs, and enhanced diagnostic capabilities. Addressing these factors could lead to earlier diagnoses, better treatment outcomes, and ultimately, reduced mortality rates in the Burgas and Yambol regions.

**Discussion**

Lung carcinoma (LC) is the first leading nosological unit in terms of morbidity and mortality in Bulgaria from oncological diseases in men and third in women. The morbidity rate for Bulgaria is 54/100,000, and the mortality rate is 44.8/100,000 population. LC is dominant among malignant diseases with a mortality rate of 17.8%, and the five-year survival rate does not exceed 15%. In this article, we make a brief comparison of the frequency of LC for Burgas and Yambol regions.

This article focuses only on the number of newly registered diseases, the age of patients, the number of deaths, and the distribution by histological type for 2018 in IOC-Burgas covering the listed areas.

With a total population of 399,000 people for Burgas and Yambol regions in Bulgaria, according to the National Statistical Institute, for the past year 2018, 146 new cases of LC were registered in IOC-Burgas. The seriousness of the disease is also characterized by its social significance related to the length of the journey to the diagnosis. Early detection remains a critical challenge, often leading to diagnoses at advanced stages where treatment options are limited and less effective.

Knowledge of the number of new LCs, their histology can help to build appropriate recommendations for a future screening mechanism and even prevention. Developing a robust screening program tailored to regional demographics could significantly improve early diagnosis rates, leading to better patient outcomes. Furthermore, public health initiatives focusing on risk factors, such as smoking cessation and environmental pollution control, are essential to reduce the incidence of LC.

According to the data that we have studied, the leading moment falls on Non-small cell lung cancer, from which the most new patients are diagnosed - squamous cell carcinoma, followed by adeno- and large cell carcinomas. The histological characteristics are clearly divided in men and women, with a clear predominance of adenocarcinomas in the latter, registered in the IOC-Burgas for 2018.

In the article, to the main types of histology, we added an additional section - Unspecified type, which includes all tumor formations in the chest cell that have not been examined histologically. Histologies with an unclear nature are also noted with the name Unspecified type. This inclusion highlights the need for improved diagnostic techniques and more comprehensive histological evaluations.

We analyzed trends in LC prevalence by histology, sex, stages, and age, in Burgas and Yambol regions with emphasis on histology and age. This detailed analysis allows for a better understanding of the demographic and biological
behavior of lung carcinoma in these regions, which is crucial for tailoring specific treatment protocols and resource allocation.

Identifying patterns in the stages of diagnosis can also help healthcare providers to develop better follow-up and monitoring strategies, ensuring timely interventions and improving the overall survival rates.

**Conclusion**

In summary, while the distribution of lung carcinoma (LC) by histology, gender, and age in the Burgas and Yambol regions aligns with expected trends, the data concerning the stage of the disease is deeply concerning. The overwhelming majority of cases are diagnosed at late stages, particularly stage IV, indicating a critical need for improved early detection strategies.

Given these findings, there is a compelling case for implementing future screening programs targeting individuals aged 60 and above in Burgas and Yambol. Early detection through screening could potentially lead to better treatment outcomes and reduced mortality rates.

Globally, the distribution of driver mutations in lung carcinoma patients includes EGFR mutations in approximately 10-15% of Western populations and up to 50% in Asian populations. ALK rearrangements occur in about 3-5% of lung cancer cases, while RET and BRAF mutations are less common, appearing in about 1-2% and 1-3% of cases respectively. PDL-1 expression, a marker for immunotherapy responsiveness, varies widely, with about 30-60% of patients showing some level of expression.

Regarding the driver mutations of lung carcinoma in the Burgas and Yambol regions, out of the 146 registered patients, 89 were tested for oncodrivers including EGFR, ALK, and PDL-1. The tests were conducted in a referring laboratory responsible for the results. Of the patients tested, four were EGFR positive, one was ALK positive, and for PDL-1, the results were as follows: 43 patients had PDL-1 levels below one percent, 38 had PDL-1 levels above one percent, and eight patients had PDL-1 levels above 50%. RET and BRAF mutations were not studied in this cohort.

These findings highlight the prevalence of significant oncodrivers in the regional population and align with global trends, emphasizing the importance of molecular testing in guiding targeted therapies. The presence of EGFR and ALK mutations, although in a small subset, underscores the necessity for incorporating targeted inhibitors in treatment protocols. Similarly, the varied expression of PDL-1 suggests that immunotherapy could be a viable option for a substantial portion of patients.

The incidence of LC by histology, sex, age, and stage will continue to change over time. Additional variations are anticipated as screening becomes more widespread. Continuous monitoring of LC rates is essential to assess the impact of these programs and to evaluate efforts aimed at reducing smoking and improving environmental conditions.

From the presented data, we can infer that patients in the age group around and over 65 years may have been exposed to numerous harmful factors during the peak of heavy industrial development in the Burgas and Yambol regions in Bulgaria. Addressing these historical exposures and implementing proactive health measures are essential steps towards reducing the burden of lung carcinoma and improving public health outcomes in these regions.

By incorporating these insights, future healthcare strategies can be better tailored to address the specific needs of the population, potentially leading to earlier diagnoses, more effective treatments, and ultimately, improved survival rates for lung carcinoma patients in Burgas and Yambol.

**Statement of Human and Animal Rights**

This study was conducted in strict accordance with ethical guidelines and standards for research involving human and animal subjects. All procedures involving human participants were performed in compliance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

For studies involving animals, all procedures were carried out in compliance with the ethical standards of the institution or practice at which the studies were conducted. The care and use of animals were in accordance with the guidelines set forth by the National Institutes of Health (NIH) for the humane treatment of laboratory animals, and all efforts were made to minimize animal suffering.

No personal information was collected or utilized in this study, ensuring the privacy and confidentiality of all participants. Informed consent was obtained from all individual participants included in the study, and the study design was reviewed and approved by the appropriate institutional review board (IRB) or ethics committee.
By adhering to these ethical standards, the study aimed to uphold the highest levels of integrity and responsibility in research involving human and animal subjects.

**Statement of Informed Consent**

This study did not involve the collection of informed consent from participants as no personal information was gathered or utilized. All data analyzed were sourced from publicly available datasets or institutional records where individual consent was either previously obtained or deemed unnecessary according to ethical guidelines.

The research was conducted in compliance with institutional and national ethical standards, ensuring that the use of data did not infringe on the privacy or rights of individuals. The ethical review board reviewed and approved the study design, confirming that the lack of direct informed consent did not compromise the ethical integrity of the research.

By adhering to these standards, the study maintained high ethical integrity, ensuring that the rights and privacy of individuals were respected throughout the research process.

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**Conflict of Interests**

Authors declare no conflict of interest.

**References**


