Rzeszów University Press 2025
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2025.1.8

*http://www.ejcem.ur.edu.pl*
*European Journal of Clinical and Experimental Medicine*
*Eur J Clin Exp Med 2025; 23 (1): 267–276*

**CASE REPORT**

# Combined COVID-19-related chronic hypoxemia and lack of screening as a double challenge for the management of asymptomatic invasive lung adenocarcinoma

Rim Bouchelaghem [1,2,3], Ahmed Amine Djedi [4], Hanène Djedi [5], Amel Boumendjel [3], Amel Chouabi [1], Nadia Hellal [1], Nadia Djendi [1]

[1] Arabi Sebti Public Hospital Establishment, COVID-19 Unit, Ain Berda, Annaba, Algeria
[2] Harcha Hacene Polyclinic, Local Public Health Establishment of El Hadjar, El Hadjar, Annaba, Algeria
[3] Laboratory of Biochemistry and Environmental Toxicology, Department of Biochemistry, Faculty of Sciences, Badji Mokhtar University, Annaba, Algeria
[4] Yachfine Medical Diagnostic Center, Annaba, Algeria
[5] Department of Medical Oncology, Cancer Center of Annaba, Annaba, Algeria

**ABSTRACT**

**Introduction and aim.** Lung adenocarcinoma (LADC) is the most diagnosed histological subtype of lung cancer and the leading cause of cancer death in men in Algeria. Defining the circumstances that preceded the diagnosis improves the management options and reduces its incidence. However, data for this critical period are lacking. We report the case of a patient whose onset of severe COVID-19 and the incidental finding of an undefined LADC overlapped and delayed care of the malignancy.

**Case description.** We present the case of a 65-year-old man, with invasive LADC discovered during a chest CT scan performed for suspected severe COVID-19. We describe the diagnostic methods and the patient. Histological examination by biopsy required to confirm diagnosis could not be performed due to chronic hypoxemia in the patient, which prevented the complete pathological diagnosis and staging of the disease.

**Conclusion.** Given the prevalence and aggressiveness of LADC in men in Algeria, our study underscores the critical need to develop screening programs, aimed at identifying the disease in asymptomatic patients, in asymptomatic patients that could significantly improve the chances of successful treatment. This is particularly important because LADC patients often develop serious pathologies that can limit their treatment options. COVID-19 serves as a stark example of such limiting interference, further highlighting the importance of early detection in the management of LADC.

**Keywords.** chest CT, COVID-19, hypoxemia, LADC, screening

## Introduction

Lung adenocarcinoma (LADC), the most common histological subtype of nonsmall cell lung cancer (NSCLC), accounts for more than 40% of cases worldwide.[1] The potential for early diagnosis of LADC (stages I and II) has been confirmed, as it is associated with a significantly good prognosis, with a survival rate of nearly 100% after surgical resection.[2] However, advanced LADC (stages III and IV), with its aggressive behavior and limited therapeutic options, remains a significant cause of

**Corresponding author:** Rim Bouchelaghem, e-mail: rimbouchelaghemk@gmail.com

Received: 2.08.2024 / Revised: 4.11.2024 / Accepted: 13.11.2024 / Published: 30.03.2025

Bouchelaghem R, Djedi AA, Djedi H, Boumendjel A, Chouabi A, Hellal N, Djendi N. Combined COVID-19-related chronic hypoxemia and lack of screening as a double challenge for the management of asymptomatic invasive lung adenocarcinoma. *Eur J Clin Exp Med.* 2025;23(1):267–276. doi: 10.15584/ejcem.2025.1.8.

cancer-related deaths worldwide, resulting in a 5-year overall survival rate of less than 75%.[3]

The circumstances of LADC diagnosis are variable. Although early stage LADC remains asymptomatic for an extended period, advanced LADC is often diagnosed with symptoms such as cough, sputum, and dyspnea.[4] In the general population, incidental finding as a scenario preceding the diagnosis of LADC has been described in many studies when this malignancy can be found at 56% to 66.9% in asymptomatic patients during the investigation of unrelated symptoms or by screening.[5] Interestingly, an estimable percentage of LADC could be discovered incidentally (9.1%).[6] This incidental finding represents an opportunity for the patient to have a better chance of recovery and allows potentially curative treatment, thus improving the overall survival rate.

Between 2020 and 2022, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significantly impacted healthcare systems worldwide.[7-9] The increased use of chest imaging to diagnose COVID-19 during the pandemic has led to the incidental finding of non-COVID-19 related lung lesions, including malignancies.[10,11] In particular, high incidental findings of LADC were also found in patients with COVID-19 at 55.6%.[12] However, the combination of COVID-19 and newly diagnosed malignancies has been described as a complicated onset since concurrent severity of COVID-19 could reduce the chances of patients starting cancer treatment before healing.[13-15] In Algeria, the final statistics reported more than 272 thousand confirmed cases of COVID-19 and over 6 thousand deaths among the Algerian population.

Lung cancer is a real scourge among the Algerian population, since it is the most prevalent cancer among men (19.5%) with high mortality (10.4%).[16] Several descriptive studies of lung cancer have been carried out in Algeria before and after the pandemic. They were mainly conducted to describe demographic, epidemiological or clinicopathological features of different types of lung cancer, including LADC, from the time of pathological diagnosis or the time of treatment in the Oncology Department.[17-25] According to the study of the Lung Cancer Registry in Algeria (LuCaReAl) study, a comprehensive research initiative on lung cancer in Algeria, LADC represents 55% of newly diagnosed lung cancer patients. The LuCaReAl study showed that the proportion of advanced stages at diagnosis was alarming, mainly due to late diagnosis.[22] Unfortunately, we were unable to find information about incidental findings of lung cancer in general or invasive LADC specifically in those reports, and studies that elaborate the clinicopathological and radiological characteristic of incidental lung cancer during the interval of imaging to pathological examination have not been addressed. Thus, the actual effect of the pandemic on the management of newly diagnosed cancer patients among Algerian patients has not been well documented so far and this lack of evidence is shared throughout the world. Therefore, more research to understand the impact of COVID-19 on this category of patients.

Here, we present an example of a case with simultaneous diagnosis of severe COVID-19 pneumonia and newly diagnosed advanced LADC. Chest computed tomography (CT) imaging of COVID-19 diagnosis revealed CT abnormalities that led to the suspicion of advanced lung cancer, which could not be identified by pathology due to COVID-19-related complications. The diagnosis, thus remaining undefined, delayed the oncologic care of the patient. This case may be representative of other cases that deserve to be studied. Additionally, we hope that this report will provide valuable information on the importance of screening for LADC at an early stage before additional medical illness overshadows the clinical picture and minimizes the chances of a cure.

**Table 1.** Laboratory data of the patient*

| Test | Day 2 | Day 6 | Day 12 | Units | Refence range |
|---|---|---|---|---|---|
| WBC | 4.49 | 11.24↑ | 11.41↑ | $10^3$/µL | 4–10.2 |
| Neutrophils | 83.9↑ | 89.0↑ | 52.9 | % | 43.5–73.5 |
| Lymphocytes | 10.9↓ | 7.61↓ | 33.8↓ | % | 15.2–43.3 |
| Red cells | 4.90 | 4.73 | 5.55 | $10^6$/µL | 3.8–6.2 |
| Monocytes | 0.23↓ | 2.68↓ | 13.3↑ | % | 3–13 |
| Hemoglobin | 10.9↓ | 11.45↓ | 11.9↓ | g/dL | 13–17.5 |
| CCMH | 31.5 | 31.7 | 31.1 | g/dL | 31–37 |
| MCV | 70.6↓ | 76.4↓ | 69.0↓ | fL | 78–100 |
| MCHC | 22.2↓ | 24.2↓ | 21.4↓ | pg | 25–34 |
| Hematocrit | 34.6↓ | 36.1↓ | 38.3↑ | g/dL | 40–52 |
| Platelets | 189 | 246.9 | 425 | $10^3$/µL | 120–450 |
| Alanine aminotransferase | 42 | 76↑ | 40 | U/L | 10–49 |
| Aspartate aminotransferase | 30 | 32 | 30 | U/L | 10–39 |
| D-dimers | 766↑ | 589.6 | 381.0 | ng/mL | >50 years, <age ×10 |
| CRP | 91.65↑ | -- | 9.67 | mg/L | <10.00 |

*↓ – the value was below normal,↑ – the value was above normal

## Description of the case

On November 28, 2021 (Day 1), a 65-year-old Caucasian male Algerian patient was referred to the emergency unit of our public hospital establishment located in Ain Berda, Annaba, due to shortness of breath, dry cough, fever, chest pain, and a low percutaneous arterial oxygen saturation ($SpO_2$) at 83% breathing on room air. Due to the endemic location and the history of contact with confirmed positive COVID-19 person a few days before presentation, he was highly suspected of getting a COVID-19 infection. However, a nasopharyngeal test for the COVID-19 antigen was negative. In fact, a serological test of COVID-19 antibodies suggested only an anterior contact with the virus. Therefore, no sufficient evidence could rule out a developing COVID-19 infection and he was admitted to an isolation box. A chest computed tomography (CT), a real-time

polymerase chain reaction (RT-PCR), and a control serological test for the SARS-CoV-2 were prescribed. A routine examination was realized (Table 1), and vital signs were regularly monitored twice (Table 2).

**Table 2.** Clinical and laboratory data of the patient during hospitalization at COVID-19 unit*

| Measure | Fasting blood glucose (g/L) at day | Postprandial plasma glucose (g/L) at night | Oxygen saturation at day (%) | Oxygen saturation at night (%) | Systolic/Diastolic blood pressure at day | Systolic/Diastolic blood pressure at night | Body temperature day/night |
|---|---|---|---|---|---|---|---|
| Reference range | 0.60–1.10 | 1.10–1.30 | > 92% | > 92% | < 90/<140 | <90/<140 | 37/37 |
| Day 4 | -- | 2.36↑ | 60↓ | 67↓ | -- | 120/60 | -/37.9 |
| Day 5 | -- | 1.48↑ | 35↓ | 48↓ | 100↑/60 | 120/70 | -/37.1 |
| Day 6 | 1.63↑ | 2.53↑ | 30↓ | 48↓ | 150↑/80 | 150↑/100 | -/36 |
| Day 7 | 2.95↑ | 2.56↑ | 59↓ | 43↓ | 120/70 | 140/80 | 39↑/39↑ |
| Day 8 | 2↑ | 2.92↑ | 45↓ | 54↓ | 150↑/80 | 140/80 | 39↑/39↑ |
| Day 9 | 2.07↑ | 1.2 | 81↓ | 83↓ | 170↑/100↑ | 130/80 | 37.1/37 |
| Day 10 | 2.12↑ | 2.26↑ | 69↓ | 76↓ | 130/80 | 150↑/90 | 37.2/37 |
| Day 11 | 3.14↑ | 2.44↑ | 73↓ | 74↓ | 140/80 | 160↑/60 | 37/37.2 |
| Day 12 | 3.34↑ | 2.97↑ | 67↓ | 76↓ | 130/80 | 130/70 | 37.1/37.1 |
| Day 13 | 2.95↑ | 2.56↑ | 67↓ | 82↓ | 120/70 | 140/70 | 37/36.9 |
| Day 14 | 1.80↑ | 1.20 | 81↓ | 82↓ | 140/70 | 140/70 | 37/36.9 |
| Day 15 | 1.87↑ | 2.7↑ | 81↓ | 71↓ | 130/70 | 130/70 | 37/37 |
| Day 16 | 1.46↑ | -- | -- | -- | 130/80 | -- | 37/36.9 |

*↓ – the value was below normal,↑ – the value was above normal, hematology and biochemistry laboratory testing were performed two times

On days 2 to 4, initial blood tests did not show a change in white cell blood count (CBC). However, there was an early inversion in the leukocyte formula (neutrophils reached 83.9% and lymphocytes decreased to 10.9%), while platelets were normal. The blood type was O-positive. We noticed low hemoglobin and hematocrit. Blood ionogram (kaliemia and chloremia) and creatinemia were normal. High levels of D-dimers (766 ng/mL) and plasmatic C-reactive protein (CRP, ~91 mg/L) were also noted. The patient presented new-onset hyperglycemia with a high HbA1c level of 7.2%. According to the Hashmi-Asif COVID-19 chart, the calculations of scoring for signs, symptoms, and blood biomarkers for the early presentation of the patient found that he was highly suspected of getting COVID-19 with a score of 24 (Table 3).[26]

On day 5, a serological conversion of COVID-19 antibodies and a positive RT-PCR for COVID-19 were obtained, indicating a developing COVID-19 infection. In addition, contrast-enhanced chest CT revealed severe involvement of both lungs with peripheral, patchy ground-glass opacities (GGO) that extended to more than 75%, consistent with a COVID-19 infection (Fig. 1A) accompanied by localized emphysema (Fig. 1B). No pneumothorax (Fig. 1A) or pulmonary embolism (Fig. 1C) were observed. However, the chest CT also showed a 46.2 × 56 × 69.3 mm solid mass (Fig. 2A and 3B) abutting the thoracic esophagus (Fig. 2B) in the right upper lobe of the lung, suggesting a malignant tumor. Two lymphadenopathies were found. The first was measured up to 0.82 × 15.3 mm and was ipsilateral subcarinal hilar, and the second node in the aortopulmonary window was measured 1.68x17.8 mm (Fig. 2C). Another finding was a 14.7 × 16.8 mm nodule in the left upper lobe, suggesting contralateral pulmonary metastases (Fig. 2D and 3C). A severe has been made of COVID-19 pneumonia diagnosis with a suspected possible advanced lung malignancy has been made.

**Table 3.** COVID-19 scoring according to Hashmi-Asif COVID-19 Assessment Chart[26,*]

| Physical signs and symptoms | Scores | | |
|---|---|---|---|
| | **Day 2** | **Day 6** | **Day 12** |
| Temperature | (39)>38 score-3 | (36)≤37 score-1 | (37.1)≤37.5 score-2 |
| Cough | Dry cough score-3 | Dry cough score-3 | Productive score-2 |
| Fatigue | >2day score-3 | >2day score-3 | >2day score-3 |
| Nausea and vomiting | Absent score-1 | Absent score-1 | Absent score-1 |
| Mucus membrane | Dry appearance score-3 | Dry appearance score-3 | Normal score-1 |
| **Total** | **13** | **11** | **9** |
| **Blood biomarkers** | | | |
| Leukocytes (3,800–1,100/μL) | 4.49 score-2 | 11.24 score-2 | 11.41 score-2 |
| Lymphocytes (1,000–3,900/μL) | 10.9 score-3 | 7.61 score-4 | 3.8 score-4 |
| Neutrophils (1,900–7,400/μL) | 83.9 score-2 | 89.0 score-2 | 52.9 score-2 |
| Platelets (150,000–400,000/μL) | 189 score-2 | 246.9 score-2 | 425 score-1 |
| *Alanine aminotransferase (10–49U/L) | 42 score-1 | 76 score-4 | 40 score-1 |
| Aspartate aminotransferase (<33 U/L) | 30 score-1 | 32 score-1 | 30 score-1 |
| **Total** | **11** | **17** | **12** |
| **Total score** | **24** | **28** | **21** |

* cumulative scoring ≥13–22/39 is considered at high risk to be diagnosed with COVID-19,
no disease ≤12, mild 13–22, moderate 23–33, severe 34–39

**Table 4.** Drugs for treatment of the patient during hospitalization*

| Drug | Hospital day | Dose | Usage |
|---|---|---|---|
| Cefotaxime | Day 6–day 10 | 1 g BID | iv |
| Ciprofloxacin | Day 11–day 16 | 200 mg BID | iv |
| Enoxaparin | Day 6–day 16 | 0.8 UI BID | sc |
| Dexamethasone | Day 6–day 16 | 8 mg BID | im |
| Budesonide | Day 6–day 16 | 1 mg BID | inh |
| Omeprazole | Day 6–day 16 | 40 mg QD | im |
| Paracetamol | Day 6–day 16 | 1 g every 8h if fever | iv |
| Macrogol 4000 | Day 6–day 16 | 10 g TID | po |
| Nicardipine | Day 11 | 1 mg once | iv |
| Neutral Protamine Hagedorn insulin | Day 6–day 16 | 18 UI BID | sc |

* QD – one a day, BID – twice a day, TID – three times a day, sc – subcutaneous, po – per os; iv – intravenously, inh – inhalation, im – intramuscular

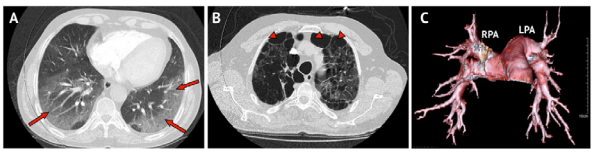


**Fig. 1.** A: Representative axial-enhanced chest CT scans (lung window) in a 65-year-old man showed a peripheral GGO pattern in the right and left middle lobes, B: Representative axial enhanced CT scans showing multiple localized emphysema and anterior pulmonary bullae (arrows headed) in bilateral upper lobes, C: The rendering of 3D pulmonary volume for enhanced CT images obtained with early injection time showed that the texture of the main pulmonary artery became thicker, presenting an intense homogenous enhancement. On the contrary, the trachea, right pulmonary artery, left pulmonary artery, segmental lobar and sous-segmental arteries were normal

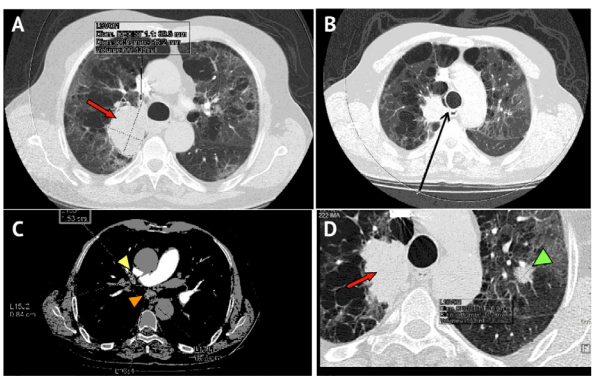


**Fig. 2.** A: Representative axial images showing a tumor process of the right upper lobe (arrow) that occupies the posterior segment and leans against the mediastinal pleura. The mass measured 46.2×56 mm in the axial plane, B: and was in close contact with the esophagus (arrow), C: CT imaging also showed that the process was associated with an ipsilateral subcarinal hilar node measuring up to 0.82×15.3 mm (yellow arrowhead) and another in the aortopulmonary window measuring 1.68×17.8 mm (orange arrowhead), D: Another suspicious pulmonary nodule was discovered in the left upper lobe measuring 14.7×16.8 mm.

The patient was transferred to the COVID-19 department to be initially treated for his severe pneumonia. With no notable medical history, he was a former smoker with a Brinkman index of 800 (40 years of smoking 20 cigarettes per day, one pack-year) and had quit smoking ten years earlier. Meanwhile, the physical examination found expectorations, marked diminished vesicular murmur throughout the chest, marked finger crabbing, constipation, and hypertension (grade 1). Low-flow oxygen therapy through a nasal cannula at 5 L/min was administered. He underwent 12 days of comprehensive treatment (Table 4) until his recovery. After completion of therapy, no apparent side effects were observed with the above drugs, except for the antibiotic agent, cefotaxime, since the patient reported dizziness and vertigo on day seven a few minutes after the injection of cefotaxime. Given its possible neurological side effects, cefotaxime was stopped and replaced with ciprofloxacin (Table 2).

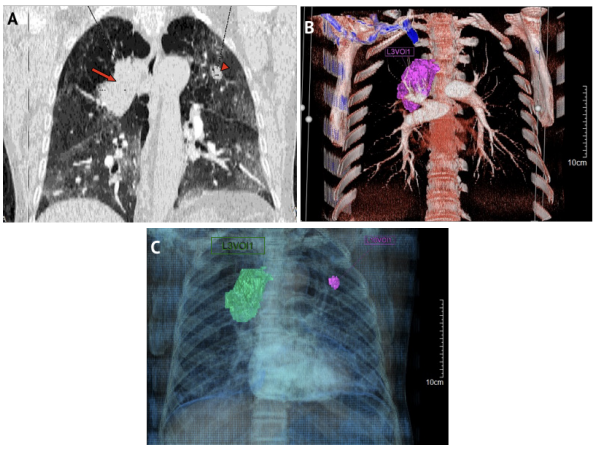


**Fig. 3.** A: Representative coronal images showing increased lung emphysema with diffuse GGO in the middle and inferior lobes and the tumor process of the right upper lobe (arrow) leaning against the mediastina and the nodule (head arrow) in the left upper lobe suggesting metastasis, B: 3D volume rendered in left rotation image from our patient demonstrating pulmonary tumor (in magenta) extended in height to 69.3 mm, C: 3D volume rendered image demonstrating right tumor (in green) and pulmonary nodule (in magenta)

From day 5 to day 8, the patient's clinical status deteriorated. He presented fever (>39°C, axillary temperature), intense chest pain, and a steady decrease in SpO2 to 30% (Table 4). Supplemental oxygen was given by combining a nasal cannula (at 5 L/min) with a nonrebreather mask (at 15 L/min). After this critical period, his symptoms were partially relieved, and we found improvement in $SpO_2$ (81–85%) breathing room air. The patient was put back on low oxygen therapy with a nasal cannula at 5 L/min. Additionally, the improvement of biological parameters was generally (except for a transient increase in alanine aminotransferase on day 6, Table 1). Applying the Hashmi-Asif Covid-19 chart again, we found that the transition in the patient's clinical status was correlated with the score values, which raised to 27 (day 6) and decreased with improving the situation of the COVID-19 situation to 21 (day 12) (Table 3).

On day 16, he was discharged from the hospital and was referred to the Oncology Department for a more extensive evaluation of the incidental finding on chest CT.

On February 2, the patient enrolled in the Oncology department of the Annaba Cancer Center. The oncologist prescribed a CT-guided biopsy to perform

a histopathological examination of the incidental mass. Unfortunately, the patient remained hypoxemic and required long-term oxygen therapy (LTOT) for approximately two months using an oxygen nasal cannula, which prevented biopsy.

One month later (March 02), a follow-up chest CT revealed a marked improvement in the GGO pattern, with diffuse bilateral interstitial lesions of sequelae appearance (data not shown). Moreover, where the CT images showed that the lymphatic nodes remained unchanged in form and size, the solid mass was found to be increased (87 mm× 60 mm ×86 mm). We thus estimated the tumor growth rate by calculating the tumor volume doubling time (TVDT) based on the chest CT scan measurements initially found before three months, using the Schwartz formula of exponential growth, where V1 and V2 were the largest diameters on the CT scan measured at two different times, and the time interval between two measurements: TVDT=(t×log2)/[log (V2/V1)].[27] We found that the TVDT for the tumor was 67 days.

On April 10, when its oxygenation status became routine, the patient underwent a CT-guided biopsy. The histopathological examination of the material collected from the solid mass confirmed a diagnosis of non-small cell poorly differentiated (high-grade) partially necrotic carcinoma of the lung. Immunohistochemistry stains showed positivity cytokeratin 7 and thyroid transcription factor-1 with negative cytokeratin 20, cluster of differentiation 56, and p40 protein. The final pathological diagnosis confirmed the mass as a solid adenocarcinoma. The oncologist prescribed substantial exams to classify the cancer. Abdominal and cerebral CT did not reveal additional features. Using technetium 99m-labeled methylene diphosphonate (99mTc-MDP), skeletal scintigraphy was performed. No other suspicious features suggestive of metastatic bone lesions were found on the abdomen, the brain, or the pelvis. According to the classification of tumor node metastases (TNM) of primary lung cancer, 8th Edition.[28] We diagnosed lung adenocarcinoma with clinical stage T3N2M0. Appropriate treatment was initiated in the Oncology department, and he began follow-up for 19 months of chemotherapy. He died in December 2023 from complicated onset and metastasis in the brain and liver.

## Discussion

Taking into account the clinical, radiological and epidemiological characteristics, this case study is consistent with previous descriptions of common severe COVID-19 worldwide. The patient presented two symptoms commonly seen among this category of patients: cough (70%) and dyspnea (66%).[29] Indeed, chest CT shows a typical GGO pattern that extends to more than 75% of his lungs, consistent with pulmonary abnormalities found in severe COVID-19 infection, even if he did not present other specific patterns, such as consolidation or pericardial effusion.[30-32] Epidemiologically, this case study shared several risk factors and comorbidities identified in the literature as factors to develop severe COVID-19. To begin with, his age, more than 60 years, is a confirmed risk factor for severe COVID-19.[33] Second, he was a former smoker with a Brinkman index greater than 400 (800), two factors that are known to cause an increased burden of severe COVID-19 outcomes, and sustained mechanical ventilation.[34-36] In addition to these factors, the patient developed a new-onset hyperglycemia described as one of the critical complications observed during patients with severe COVID-19 (41 %).[37,38] Furthermore, of all comorbidities he presented, the LADC was the most burdensome risk factor for COVID-19 severity.[39,40] Regarding this malignancy, we found a gap in the data that described the incidental finding of lung cancer during COVID-19 infection, including tumor characteristics and severity of COVID-19, as well as the course of events from the first imaging to oncology management. Wang and colleagues study conducted in China in 2024 was the only study that reported the incidence of lung cancer as an incidental finding since they identified that among 24390 patients who underwent a chest CT for diagnosis of COVID-19, 0.3% had undefined lung cancer. Interestingly, LADC was the predominant histological type discovered in this cohort, accounting for 55.6%.[12] However, this study relied on data from an epidemiological analysis that lacked several clinicopathological characteristics and did not capture the complete clinical picture of a given case, as mentioned in our study. In addition to this single large-scale study, only one clinical case, presented by Iadevaia and her co-workers, reported incidental lung cancer with severe COVID-19 was shown to be a 42-year-old female, non-smoker.[11] The patient has improved clinically and physically after eight days of onset without long-term COVID-19 complications.[11] Her oncological treatment appears to have been timely, as she promptly received a pathological diagnosis of a micropapillary infiltrating LADC and began chemotherapy. In comparison, although our case recovered from the severe infection and was discharged after ten days of hospitalization, the pathological diagnosis of the suspected LADC was unfortunately delayed by three months. During this time, he experienced prolonged hypoxemia that required LTOT. This finding is consistent with many cohort studies, which have described the persistence of chronic hypoxemia in the early postacute phase of COVID-19, requiring LTOT up to six months after discharge.[41,42] In addition, hypoxemia related to COVID-19 has been proven to result from damage to both the pulmonary parenchyma and vasculature.[43] In this case, hypoxemia should be added to

the list of factors that negatively affect lung cancer care in COVID-19-affected patients, mainly as a barrier to accessing definitive cancer diagnosis for the patient, as mentioned by Malalasekera and colleagues or by delaying the timely diagnosis and staging of the disease, according to Barata and colleagues.[44-46]

Consistent with previous studies conducted before the pandemic, we found that the solid LADC reported here presented typical aggressive clinicopathologic features, including a larger tumor size at initial presentation, lymph node metastasis, lymphovascular and pleural invasion, as well as a fast growth.[47-49] Nevertheless, the tumor presented a TVDT of 67 days that was shorter than the median TDVT found in the literature for solid LADC ranging from 140 days to 229 days.[50,51] LADC size is closely related to the hypoxic state of the tumor microenvironment.[52] Interestingly, hypoxia was shown to be a common characteristic shared in both COVID-19 and LADC; both pathologies are known to harbor hypoxia-associated genetic signatures that prompt altered energy metabolism.[53-55] We can hypothesize that hypoxemia as a long-term COVID-19-related complication could accelerate LADC growth rate of LADC. Future studies are needed to confirm this hypothesis.

Before the COVID-19 pandemic, many countries have established recommendations to define the intervals to be respected between the incidental finding of NSCLC and other points in the care trajectory. For example, the suggested mean time from suspicious imaging to pathological diagnosis should be between 14 and 21 days, while the median time from the first abnormal radiographic finding to treatment should be between 52 and 84 days.[56-59] Considering that LADC can get a rapid TVDT, even patients newly diagnosed with an early LADC can be shifted to an invasive one without rapid management due to interfering factors during the imaging-pathological examination interval. A more comprehensive study is necessary to provide more details about the factors impacting the management of LADC.

Incidental LADC detection is common and does not present a novelty. However, our study's strength is that it constitutes the first report of incidental discovery of invasive LADC in Algeria. Therefore, it is interesting because it makes us aware that incidental discovery is not well described and reported. In fact, clinical scenarios after incidental diagnoses of lung cancer, as well as their radiological characteristics, are lacking in Algeria, both before and after the pandemic period. This may impact the evaluation of specific variations in this group of patients that could affect the management of LADC, especially in the presence of comorbidities such as COVID-19. In this case, LADC growth is an evolving process and guidelines may be suggested to plan an appropriate follow-up examination and management. We can advise physicians to use the European collaborative group report for individual incidental findings statements as an evidence-based approach for reporting and managing incidental findings.[60] A CT follow-up examination can explore the natural chronologic evolution of LADC. Low-dose chest CT (LDCT) can be helpful in the first diagnosis and in predicting tumor growth patterns and aggressiveness of suspected malignant suspected LADC.[61] We invite other teams to describe their findings on incidental lung cancer to improve our understanding and improve patient outcomes.

According to the National Anticancer Plan, interventions to reduce the burden of lung cancer in Algeria are limited to controlling tobacco consumption of the risk factor tobacco.[20] However, given the high incidence of invasive LADC among the Algerian population, which reduces the chances of treatment success and survival, the health system must make judicious decisions to reinforce this preventive approach with an early diagnosis procedure to reduce the incidence of aggressive forms. Thus, screening should be an obvious first choice for LADC early detection. Indeed, it is worth noting that the observed decrease in mortality from pulmonary malignancy in developed countries is due mainly to the increase in lung cancer screening in smokers and non-smokers with other risk factors.[62,63] However, it is noticeable that more different screening methods can be applied if chest-X-ray or sputum is a method that has proved ineffective and that is not recommended as a screening tool. LDCT remains the only possibility. Several screening studies, such as the National Lung Screening Trial (NLST) and the NELSON Trial, have shown the effectiveness of LDCT in improving the early diagnosis of lung cancer but also in reducing specific lung cancer mortality (20% at 6.5 years in NLST, 24% at ten years in NELSON).[64,65] Interestingly, LDCT screening is effective in detecting LADC. In 3339 individual screening trials, lung cancer has found a ratio for cancer detection ratio, with LADC accounting for 88% (40% early stage and 53% invasive).[66] Unfortunately, Algeria does not have a national lung cancer screening program. LDCT screening can be generally disseminated in eligible Algerian populations such as high-risk smokers. However, since LADC is also related to non-cigarette risk factors, considerations should be taken to increase screening, with proper guidelines for implemented LDCT screening involving occupational exposure and other risk factors.[67] In the absence of a formal screening program, we can advise physicians to use the European Collaborative Group report for individual reporting of incidental findings that can be followed during incidental lung cancer discovery as an evidence-based approach for reporting and managing incidental findings.[60]

It should be noted that our study has a few limitations since it represents an isolated case of inciden-

tal cancer during COVID-19 hospitalization in our facility. This makes the result less generalizable. Although the current study describes the characteristics of COVID-19 with LADC, we cannot emphasize whether the COVID-19 lockdown negatively affected its onset. We encourage the community to address the same studies that require large-scale and longer-term observation. We, therefore, propose to examine the frequency of incidental diagnosis among an incident cohort of patients with lung cancer, compare the characteristics of incidentally versus nonincidentally diagnosed patients, and examine common pathways and mechanisms that led to the incidental diagnosis of cancer using registries.

## Conclusion

Considering the high incidence of aggressive LADC in Algeria, more attention should be paid to identifying new procedures for its management. The described case shows how important it is to spread the screening principles and the need for studies about incidentally findings of the disease, especially among former tobacco people and professionals from high-risk groups in Algeria. We make a call to highlight the main circumstances leading to the late diagnosis of invasive lung cancer, particularly the lack of screening. Our case study illustrates the importance of implementing a large-scale LDCT screening program for lung cancer in Algeria, which can improve options for early lung cancer detection and follow-up for diagnosis and treatment.

In addition, this description underlines the critical importance of conducting more in-depth studies to obtain more information on the clinicopathological features of incidental findings. These studies are essential not only to define the incidental discovery of cases of lung cancer during the COVID-19 pandemic retrospectively but also to evaluate the long-term effects of the COVID-19 pandemic, such as delayed diagnoses and changes in patient care, on this population. The urgency and importance of this research cannot be overstated.

## Declarations

***Funding***

This research did not receive a specific grant from any funding agency in the public, commercial or not-for-profit sectors.

***Author contributions***

Conceptualization, R.B.; Methodology, R.B, A.A.D. and A.C; Software, R.B. and A.A.D; Validation, R.B., N.D. and N.H.; Formal Analysis, R.B., A.A.D. and H.D; Investigation, R.B.; Resources, R.B., A.A.D. and H.D; Data Curation, R.B; A.A.D. and H.D; Writing – Original Draft Preparation, R.B.; Writing – Review & Editing, R.B., H.D. and A.M.; Visualization, R.B, H.D. and A.B.; Supervision, R.B.; Project Administration, R.B.

***Conflicts of interest***

The authors declare no conflict of interest in connection with the study.

***Data availability***

No additional source data are required.

***Ethics approval***

This study was approved by the institutional ethics committee of the Public Hospital Establishment and the Ethics Committee of the Cancer Center of Annaba.

## References

1. Myers DJ, Wallen JM. Lung Adenocarcinoma. *StatPearls*. 2024.
2. Xi J, Yin J, Liang J, et al. Prognostic Impact of Radiological Consolidation Tumor Ratio in Clinical Stage IA Pulmonary Ground Glass Opacities. *Front Oncol*. 2021;11:616149. doi: 10.3389/fonc.2021.616149
3. Weng CF, Huang CJ, Huang SH, et al. New International Association for the Study of Lung Cancer (IASLC) Pathology Committee Grading System for the Prognostic Outcome of Advanced Lung Adenocarcinoma. *Cancers (Basel)*. 2020;12(11):3426. doi: 10.3390/cancers12113426
4. Casal-Mourino A, Ruano-Ravina A, Lorenzo-Gonzalez M, et al. Epidemiology of stage III lung cancer: frequency, diagnostic characteristics, and survival. *Transl Lung Cancer Res*. 2021;10(1):506-518. doi: 10.21037/tlcr.2020.03.40
5. Quadrelli S, Lyons G, Colt H, Chimondeguy D, Buero A. Clinical characteristics and prognosis of incidentally detected lung cancers. *Int J Surg Oncol*. 2015;2015:287604. doi: 10.1155/2015/287604
6. Kocher F, Lunger F, Seeber A, et al. Incidental Diagnosis of Asymptomatic Non-Small-Cell Lung Cancer: A Registry-Based Analysis. *Clin Lung Cancer*. 2016;17(1):62-67. doi: 10.1016/j.cllc.2015.08.006
7. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. doi: 10.1001/jama.2020.1585
8. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733. doi: 10.1056/NEJMoa2001017
9. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg*. 2020;76:71-76. doi: 10.1016/j.ijsu.2020.02.034
10. Guillo E, Bedmar Gomez I, Dangeard S, et al. COVID-19 pneumonia: Diagnostic and prognostic role of CT based on a retrospective analysis of 214 consecutive patients from Paris, France. *Eur J Radiol*. 2020;131:109209. doi: 10.1016/j.ejrad.2020.109209
11. Iadevaia C, Perrotta F, Mazzeo G, et al. Incidental diagnosis of lung adenocarcinoma following coronavirus OC

43 severe pneumonia. *Monaldi Arch Chest Dis*. 2020;90(3) doi: 10.4081/monaldi.2020.1313
12. Wang P, Martel P, Hajjam ME, et al. Incidental diagnosis of lung cancer on chest CT scan performed for suspected or documented COVID-19 infection. *Respir Med Res*. 2024;85:101084. doi: 10.1016/j.resmer.2024.101084
13. Madan A, Siglin J, Khan A. Comprehensive review of implications of COVID-19 on clinical outcomes of cancer patients and management of solid tumors during the pandemic. *Cancer Med*. 2020;9(24):9205-9218. doi: 10.1002/cam4.3534
14. Zhang Y, Li J, Li ZK, et al. Impact of Coronavirus Disease 2019 on Clinical Characteristics in Patients With Lung Cancer: A Large Single-Centre Retrospective Study. *Front Oncol*. 2021;11:693002. doi: 10.3389/fonc.2021.693002
15. Mojsak D, Debczynski M, Kuklinska B, et al. Impact of COVID-19 in Patients with Lung Cancer: A Descriptive Analysis. *Int J Environ Res Public Health*. 2023;20(2)1583. doi: 10.3390/ijerph20021583
16. IARC. Cancer today. https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf. Accessed September 5, 2024.
17. Bekara MEA, Djebbar A, Sebaihia M, Bouzeghti MEA, Badaoui L. Bayesian spatio-temporal analysis of the incidence of lung cancer in the North West of Algeria, 2014-2020. *Spat Spatiotemporal Epidemiol*. 2023;45:100583. doi: 10.1016/j.sste.2023.100583
18. Benarba B, Meddah B, Hamdani H. Cancer incidence in North West Algeria (Mascara) 2000-2010: results from a population-based cancer registry. *EXCLI J*. 2014;13:709-723.
19. Lahmadi M, Beddar L, Ketit S, Makhbouche T, Laouar N, Filali T. Clinicopathological characteristics and prognosis of non-small cell lung cancer in Algeria: a single-center retrospective study. *BMC Cancer*. 2024;24(1):946. doi: 10.1186/s12885-024-12709-5
20. Adda Bounedjar MAM, Hassina Idir, and Nassiba Heba. General Oncology Care in Algeria. *Cancer in the Arab World*. Springer, 2022;2. doi: 10.1007/978-981-16-7945-2
21. Jazieh AR, Bounedjar A, Abdel-Razeq H, et al. Impact of COVID-19 on Management and Outcomes of Oncology Patients: Results of MENA COVID-19 and Cancer Registry (MCCR). *J Immunother Precis Oncol*. 2024;7(2):82-88. doi: 10.36401/JIPO-23-38
22. Bounedjar A, Benkali R, Badoui L, et al. Incidence of lung cancer in males and females in Algeria: The lung cancer registry in Algeria (LuCaReAl). *Cancer Epidemiol*. 2020;69:101799. doi: 10.1016/j.canep.2020.101799
23. Ketfi A, Zanoun N, Laouedj I, Gharnaout M, Fraga S. [Primary lung cancer and occupational exposure in a North African population]. *Pan Afr Med J*. 2020;37:120. doi: 10.11604/pamj.2020.37.120.21755
24. Belkacemi Y, Grellier N, Ghith S, et al. A review of the international early recommendations for departments organization and cancer management priorities during the global COVID-19 pandemic: applicability in low- and middle-income countries. *Eur J Cancer*. 2020;135:130-146. doi: 10.1016/j.ejca.2020.05.015
25. Hamdi Cherif M, Serraino D, Mahnane A, et al. Time trends of cancer incidence in Setif, Algeria, 1986-2010: an observational study. *BMC Cancer*. 2014;14:637. doi: 10.1186/1471-2407-14-637
26. Hashmi HAS, Asif HM. Early Detection and Assessment of Covid-19. *Front Med (Lausanne)*. 2020;7:311. doi: 10.3389/fmed.2020.00311
27. Schwartz M. A biomathematical approach to clinical tumor growth. *Cancer*. 1961;14:1272-1294. doi: 10.1002/1097-0142(196111/12)14:6<1272::aid-cncr2820140618>3.0.co;2-h
28. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8(th) lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. *Quant Imaging Med Surg*. 2018;8(7):709-718. doi: 10.21037/qims.2018.08.02
29. Luo J, Rizvi H, Preeshagul IR, et al. COVID-19 in patients with lung cancer. *Ann Oncol*. 2020;31(10):1386-1396. doi: 10.1016/j.annonc.2020.06.007
30. Li K, Wu J, Wu F, et al. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. *Invest Radiol*. 2020;55(6):327-331. doi: 10.1097/RLI.0000000000000672
31. Brumini I, Dodig D, Zuza I, et al. Validation of Diagnostic Accuracy and Disease Severity Correlation of Chest Computed Tomography Severity Scores in Patients with COVID-19 Pneumonia. *Diagnostics (Basel)*. 2024;14(2):148. doi: 10.3390/diagnostics14020148
32. Ramdani H, Allali N, Chat L, El Haddad S. Covid-19 imaging: A narrative review. *Ann Med Surg (Lond)*. 2021;69:102489. doi: 10.1016/j.amsu.2021.102489
33. Romero Starke K, Reissig D, Petereit-Haack G, Schmauder S, Nienhaus A, Seidler A. The isolated effect of age on the risk of COVID-19 severe outcomes: a systematic review with meta-analysis. *BMJ Glob Health*. 2021;6(12):e006434. doi: 10.1136/bmjgh-2021-006434
34. Zhang H, Ma S, Han T, et al. Association of smoking history with severe and critical outcomes in COVID-19 patients: A systemic review and meta-analysis. *Eur J Integr Med*. 2021;43:101313. doi: 10.1016/j.eujim.2021.101313
35. Onishi H, Yamamura O, Sakamaki I, Miyashita H, Iwasaki H. Can the Brinkman Index Predict the Need for Treatment in Patients With COVID-19? *Asia Pac J Public Health*. 2022;34(6-7):692-694. doi: 10.1177/10105395221113773
36. Gallus S, Scala M, Possenti I, et al. The role of smoking in COVID-19 progression: a comprehensive meta-analysis. *Eur Respir Rev*. 2023;32(167):220191. doi: 10.1183/16000617.0191-2022
37. Le VT, Ha QH, Tran MT, Le NT, Le VT, Le MK. Hyperglycemia in Severe and Critical COVID-19 Patients: Risk Factors and Outcomes. *Cureus*. 2022;14(8):e27611. doi: 10.7759/cureus.27611

38. Feng Y, Ling Y, Bai T, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. *Am J Respir Crit Care Med*. 2020;201(11):1380-1388. doi: 10.1164/rccm.202002-0445OC
39. Lemos AEG, Silva GR, Gimba ERP, Matos ADR. Susceptibility of lung cancer patients to COVID-19: A review of the pandemic data from multiple nationalities. *Thorac Cancer*. 2021;12(20):2637-2647. doi: 10.1111/1759-7714.14067
40. Chen L, Liu Y, Wu J, et al. Lung adenocarcinoma patients have higher risk of SARS-CoV-2 infection. *Aging (Albany NY)*. 2021;13(2):1620-1632. doi: 10.18632/aging.202375
41. Weerahandi H, Hochman KA, Simon E, et al. Post-Discharge Health Status and Symptoms in Patients with Severe COVID-19. *J Gen Intern Med*. 2021;36(3):738-745. doi: 10.1007/s11606-020-06338-4
42. Loerinc LB, Scheel AM, Evans ST, Shabto JM, O'Keefe GA, O'Keefe JB. Discharge characteristics and care transitions of hospitalized patients with COVID-19. *Healthc (Amst)*. Mar 2021;9(1):100512. doi: 10.1016/j.hjdsi.2020.100512
43. Steinbeis F, Thibeault C, Doellinger F, et al. Severity of respiratory failure and computed chest tomography in acute COVID-19 correlates with pulmonary function and respiratory symptoms after infection with SARS-CoV-2: An observational longitudinal study over 12 months. *Respir Med*. 2022;191:106709. doi: 10.1016/j.rmed.2021.106709
44. Passaro A, Bestvina C, Velez Velez M, Garassino MC, Garon E, Peters S. Severity of COVID-19 in patients with lung cancer: evidence and challenges. *J Immunother Cancer*. 2021;9(3):e002266. doi: 10.1136/jitc-2020-002266
45. Malalasekera A, Nahm S, Blinman PL, Kao SC, Dhillon HM, Vardy JL. How long is too long? A scoping review of health system delays in lung cancer. *Eur Respir Rev*. 2018;27(149):180045. doi: 10.1183/16000617.0045-2018
46. Barata F, Fidalgo P, Figueiredo S, Tonin FS, Duarte-Ramos F. Limitations and perceived delays for diagnosis and staging of lung cancer in Portugal: A nationwide survey analysis. *PLoS One*. 2021;16(6):e0252529. doi: 10.1371/journal.pone.0252529
47. Cha MJ, Lee HY, Lee KS, et al. Micropapillary and solid subtypes of invasive lung adenocarcinoma: clinical predictors of histopathology and outcome. *J Thorac Cardiovasc Surg*. 2014;147(3):921-928. doi: 10.1016/j.jtcvs.2013.09.045
48. Xu L, Tavora F, Burke A. Histologic features associated with metastatic potential in invasive adenocarcinomas of the lung. *Am J Surg Pathol*. 2013;37(7):1100-1108. doi: 10.1097/PAS.0b013e31827fcf04
49. Chen PH, Chang KM, Tseng WC, Chen CH, Chao JI. Invasiveness and surgical timing evaluation by clinical features of ground-glass opacity nodules in lung cancers. *Thorac Cancer*. 2019;10(11):2133-2141. doi: 10.1111/1759-7714.13199
50. Henschke CI, Yankelevitz DF, Yip R, et al. Lung cancers diagnosed at annual CT screening: volume doubling times. *Radiology*. 2012;263(2):578-583. doi: 10.1148/radiol.12102489
51. Park S, Lee SM, Kim S, et al. Volume Doubling Times of Lung Adenocarcinomas: Correlation with Predominant Histologic Subtypes and Prognosis. *Radiology*. 2020;295(3):703-712. doi: 10.1148/radiol.2020191835
52. Mo Z, Yu L, Cao Z, Hu H, Luo S, Zhang S. Identification of a Hypoxia-Associated Signature for Lung Adenocarcinoma. *Front Genet*. 2020;11:647. doi: 10.3389/fgene.2020.00647
53. Gao L, Li GS, Li JD, et al. Identification of the susceptibility genes for COVID-19 in lung adenocarcinoma with global data and biological computation methods. *Comput Struct Biotechnol J*. 2021;19:6229-6239. doi: 10.1016/j.csbj.2021.11.026
54. Ullah MA, Alam S, Moin AT, Ahamed T, Shohael AM. Risk factors and actionable molecular signatures in COVID-19-associated lung adenocarcinoma and lung squamous cell carcinoma patients. *Comput Biol Med*. 2023;158:106855. doi: 10.1016/j.compbiomed.2023.106855
55. Serebrovska ZO, Chong EY, Serebrovska TV, Tumanovska LV, Xi L. Hypoxia, HIF-1alpha, and COVID-19: from pathogenic factors to potential therapeutic targets. *Acta Pharmacol Sin*. 2020;41(12):1539-1546. doi: 10.1038/s41401-020-00554-8
56. BTS. BTS recommendations to respiratory physicians for organising the care of patients with lung cancer. The Lung Cancer Working Party of the British Thoracic Society Standards of Care Committee. *Thorax*. 1998;53(1):1-8. doi: 10.1136/thx.53.suppl_1.s1
57. Malalasekera A, Blinman PL, Dhillon HM, et al. Times to Diagnosis and Treatment of Lung Cancer in New South Wales, Australia: A Multicenter, Medicare Data Linkage Study. *J Oncol Pract*. 2018;14(10):621-630. doi: 10.1200/JOP.18.00125
58. Hermens RP, Ouwens MM, Vonk-Okhuijsen SY, et al. Development of quality indicators for diagnosis and treatment of patients with non-small cell lung cancer: a first step toward implementing a multidisciplinary, evidence--based guideline. *Lung Cancer*. 2006;54(1):117-124. doi: 10.1016/j.lungcan.2006.07.001
59. Vidaver RM, Shershneva MB, Hetzel SJ, Holden TR, Campbell TC. Typical Time to Treatment of Patients With Lung Cancer in a Multisite, US-Based Study. *J Oncol Pract*. 2016;12(6):643-653. doi: 10.1200/JOP.2015.009605
60. O'Dowd EL, Tietzova I, Bartlett E, et al. ERS/ESTS/ESTRO/ESR/ESTI/EFOMP statement on management of incidental findings from low dose CT screening for lung cancer. *Eur J Cardiothorac Surg*. 2023;64(4)ezad302. doi: 10.1093/ejcts/ezad302
61. Min JH, Lee HY, Lee KS, et al. Stepwise evolution from a focal pure pulmonary ground-glass opacity nodule into an invasive lung adenocarcinoma: an observation for more than 10 years. *Lung Cancer*. 2010;69(1):123-126. doi: 10.1016/j.lungcan.2010.04.022
62. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the

TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007;2(8):706-714. doi: 10.1097/JTO.0b013e31812f3c1a

63. Rates ACSLCS. https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging/survival-rates.html. Accessed September 16, 2024
64. Gareen IF, Gutman R, Sicks J, et al. Significant Incidental Findings in the National Lung Screening Trial. *JAMA Intern Med*. 2023;183(7):677-684. doi: 10.1001/jamainternmed.2023.1116
65. Dawson Q. NELSON trial: reduced lung-cancer mortality with volume CT screening. *Lancet Respir Med*. 2020;8(3):236. doi: 10.1016/S2213-2600(20)30059-X
66. Chen CY, Chen CH, Shen TC, et al. Lung cancer screening with low-dose computed tomography: Experiences from a tertiary hospital in Taiwan. *J Formos Med Assoc*. 2016;115(3):163-170. doi: 10.1016/j.jfma.2015.11.007
67. Pinsky PF. Lung cancer screening with low-dose CT: a world-wide view. *Transl Lung Cancer Res*. 2018;7(3):234-242. doi: 10.21037/tlcr.2018.05.12