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COVID-19 : EFFECT ON LUNG CANCER PROGRESS

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Review Article

ABSTRACT

The advent of corona virus disease 2019 (COVID-19) has caused confusion, changed people's living conditions, including commuting restrictions, fear of disease transmission, The corona virus is "Aladdin's meracle lamp" for lungs cancer, this is a huge curse for lung cancer patients. As the Root of entry of Virus is Respiratory tract,Complicaion arises in lungs.
The risk of chemotherapy-related infections increases for such patients. "Targeted therapy is generally safe while the potential interaction between immunotherapy and COVID-19 remains unknown at present". The Present article focus on Different Immunological fact related to COVID-19 and Physiological degradation of Lungs by Corona Virus and Effect on Lung cancer.

Keywords: Corona virus; chemotherapy; malignancy; infection; physiology; pathogenesis.

1. INTRODUCTION

Cancer patients represent a vulnerable population for COVID-19 illness. We aimed to analyze outcomes of lung cancer patients affected by COVID-19 in a tertiary hospital of a high-incidence region during the pandemic.COVID-19 can cause a range of breathing problems, from mild to critical. Older adults and people who have other health conditions like heart disease, cancer, and diabetes may have more serious symptoms [1,2].

Lung cancer is the largest cause of cancer deaths in the world and there is no doubt that the COVID-19 pandemic has had a dramatic impact on the early detection of lung and other cancers [3-6]. In the first few months of the pandemic, screening programmes in many countries were suspended, diagnostic tests and procedures deferred and only the most urgent symptomatic cases were referred for diagnostic f7llow-up [1].

When the virus gets in your body, it comes into contact with the mucous membranes that line your nose, mouth, and eyes. The virus enters a healthy cell and uses the cell to make new virus parts. It multiplies, and the new viruses infect nearby cells.Think of your respiratory tract as an upside-down tree [8-11]. The trunk is your trachea, or windpipe. It splits into smaller and smaller branches in your lungs. At the end of each branch are tiny air sacs called alveoli. This is where oxygen goes into your blood and carbon dioxide comes out.

The new coronavirus can infect the upper or lower part of your respiratory tract. It travels down your

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airways. The lining can become irritated and inflamed. In some cases, the infection can reach all the way down into your alveoli. COVID-19 is a new condition, and scientists are learning more every day about what it can do to your lungs. They believe that the effects on your body are similar to those of two other coronavirus diseases, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [12-14].

Learning Lessons from Across Europe – Prioritising Lung Cancer after COVID-19, highlights how, in just 12 months of the pandemic, lung cancer progress in diagnosis has been pushed back, with further impact on treatment likely the longer the pandemic continues [15,16].

In response to the fact that over 40% of countries reported a complete or partial disruption to lung cancer services due to the pandemic [17], the Lung Ambition Alliance and the World Economic Forum have launched a series of recommendations for governments and regulators on how to improve the short- and long-term resilience of lung cancer services, to ultimately improve patient outcomes.

First COVID-19 confirmed case in Madrid was detected on February 25th, 2020. Since then and until May 12th, 2020 there have been 65,269 confirmed cases by SARS-CoV-2 PCR, with 41,856 hospitalizations, 3,555 ICU admissions, and 8,760 reported deaths by COVID-19 in Madrid (1). A preliminary seroprevalence study revealed a 11.3% prevalence in Madrid by measuring IgG antibodies anti-SARS-CoV-2, accounting for one of the most prevalent regions in Spain [18]. National lockdown in Spain took place on March, 15th 2020.

Even when most patients develop mild symptoms from COVID-19, or are asymptomatic, approximately 20% develop severe symptoms [7,19]. These severe clinical manifestations consist on acute respiratory distress syndrome (ARDS), septic shock, and multiorgan failure. In the pathogenic of severe COVID-19 cases underlies a cytokine release syndrome (CRS) in which interleukin 6 (IL-6) plays a central role [20,21]. In severe cases, admission in intensive care units (ICU) and mechanical ventilation (MV) is needed. No specific antiviral or anti-inflammatory therapy has demonstrated to date any clinical efficacy to reduce mortality of COVID-19. Most treatments remain experimental, and supportive care adapted to the clinical situation of the patient remains the basis of COVID-19 management. For the overall population, mortality for COVID-19 is estimated in 1–3% [4].

Cancer patients and cancer survivors represent a vulnerable population for COVID-19. Overall prevalence of COVID-19 in cancer patients is estimated on 1–6

2. CORONA INFECTION MAGNITUDE

2.1 Mild and Moderate Cases

As the infection travels your respiratory tract, your immune system fights back. Your lungs and airways swell and become inflamed. This can start in one part of your lung and spread.About 80% of people who have COVID-19 get mild to moderate symptoms. You may have a dry cough or a sore throat. Some people have pneumonia, a lung infection in which the alveoli are inflamed.

Doctors can see signs of respiratory inflammation on a chest X-ray or CT scan. On a chest CT, they may see something they call “ground-glass opacity” because it looks like the frosted glass on a shower door [20].

2.2 Severe Cases

About 14% of COVID-19 cases are severe, with an infection that affects both lungs. As the swelling gets worse, your lungs fill with fluid and debris.

You might also have more serious pneumonia. The air sacs fill with mucus, fluid, and other cells that are trying to fight the infection. This can make it harder for your body to take in oxygen. You may have trouble breathing or feel short of breath. You may also breathe faster.

If your doctor takes a CT scan of your chest, the opaque spots in your lungs look like they start to connect to each other.

2.3 Critical Cases

In critical COVID-19 -- about 5% of total cases -- the infection can damage the walls and linings of the air sacs in your lungs. As your body tries to fight it, your lungs become more inflamed and fill with fluid. This can make it harder for them to swap oxygen and carbon dioxide.You might have severe pneumonia or acute respiratory distress syndrome (ARDS). In the most critical cases, your lungs need help from a machine called a ventilator to do their job.

There’s evidence that 20-30% of the critically ill patients can develop clots in the lungs, heart, brain and legs, some of which are life threatening. A few

people have needed lung transplants because of severe tissue damage from COVID-19 [21].

2.4 Effect of Corona Virus on Lungs Lungs

The coronavirus that causes COVID-19 is still very new to us, and there's a lot to learn about what the virus actually does to a person's body — including how it affects the lungs.

We do know that COVID-19 is an upper respiratory illness that infected people can easily spread as they breathe, speak, clear their throat, or cough near someone else — even if they don't know they have it. It's why we should all be social distancing and wearing masks while outside our homes.

After gaining entry through either the nose or mouth, the virus travels to the chest and begins to cause injury to the respiratory system," says Dr. Tim Connolly, pulmonologist at Houston Methodist. "The extent of this damage varies from person to person, with some people experiencing only mild damage to the airways. Others, however, suffer damage that's much more severe, which can sometimes even be life-threatening." [22].

What happens to the lungs during a mild case of COVID-19?

Once in the chest, the virus begins to impact a person's airways — causing inflammation. As inflammation increases, a barking, dry cough that sounds and feels like asthma develops. In addition, this can cause chest tightness or deep pain while breathing.

Even though it's generally mild for some people, the swelling and tightness that results from airway inflammation is essentially like having a sprained windpipe. Think of it like having a sprained ankle, but the effects and discomfort that come with having a sprain are felt inside of your chest.

Change of Morphology to the lungs during a more severe case of COVID-19 :

For some people, the infection becomes more serious and the lung tissue itself becomes swollen and filled with fluid and debris from dead cells — which is clinically referred to as pneumonia.

This fluid build-up can affect a person's oxygen levels, and pneumonia can be mild, moderate, severe or even life-threatening, depending on how impaired gas transfer becomes and how difficult it is to breathe.

If the transfer of oxygen into the blood stream is reduced, a person will often need supplemental oxygen and very close monitoring in a hospital setting.

In very serious cases, a person may need to be placed on ventilator support in the ICU.

Early on during the pandemic, there were a lot of unknowns about how contagious the virus could become during various medical interventions. Time and experience has taught us a lot about this virus, and now we're able to more safely use several noninvasive breathing and oxygen devices, as well as techniques such as prone positioning before we have to resort to full life support with a ventilator [23].

2.5 Covid-19 and Pre existing Lungs Disease

A person with pre-existing lung diseases, such as asthma or COPD, generally has less respiratory reserve than a person with no lung issues. Because of this, these individuals are more vulnerable and generally have a harder time if their lungs are impacted by an acute infection.

However, while we initially assumed that people with lung diseases would be disproportionately impacted by this virus, what we're actually seeing in our patient population is that COVID-19 appears to be targeting other groups more consistently — particularly people who are obese, diabetic or have vascular disease such as hypertension.

We still don't fully understand why people with preexisting lung conditions don't make up a larger majority of current COVID-19 cases as initially anticipated. Preliminary data suggest that people with asthma may make less of the receptor that the virus uses to invade the body, called ACE2, making it more difficult for the virus to gain entry into the host. In addition, ongoing maintenance therapy with inhaled steroids, such as budesonide, may also confer an advantage for people with chronic lung conditions.

Does COVID-19 have long-term effects on the lungs?
This new virus has only been around for about six months, so it's much too early to make definitive statements about the potential long-term effects it [24].

2.6 Corona Virus Effect for Lung Cancer

1. How has the COVID-19 pandemic affected the care and quality of life of patients with lung cancer?

Patients with lung cancer often present for treatment at advanced stages and require frequent visits, but the

cancer care delivery system has been adversely affected because of lockdown. At one point, chemotherapy, radiotherapy, palliative care, and follow-ups for patients with lung cancer were in standstill mode. While the situation is improving overall, diagnosis is delayed as bronchoscopy and other interventional procedures have been deferred [25].

In addition, nationwide lockdown has restricted access to transportation and flight services. Patients in rural areas are suffering as they are unable to access the cancer centers that are primarily located in urban areas. Delays and changes in treatment are causing anxiety and distress among patients with lung cancer. Limited availability of intensive care facilities because of the needs of patients with has further strained the care of patients with lung cancer when aggressive curative treatment in the form of surgical resection is required [19].

As the incidence of COVID-19 has decreased in our area, the services have resumed, although below previous capacity. Surgical capacity has decreased in order to minimize patient exposure to COVID-19. Chemotherapy infusion capacity has decreased in order to maintain safe social distancing [26-28]. Clinic visit capacity has decreased for the same reason. The one positive result of all of these changes is that the lower volumes have decreased visit and infusion wait times because of increased efficiency, and this has had a significant positive effect on quality of life for patients [29,0].

2. What are some ways in which these issues are being addressed in practice in terms of both treatment and patient safe?

Various lung cancer associations have issued guidelines on lung cancer care during the pandemic which depend on therapeutic intent and treatment benefits, considering the patient's age, various comorbidities, and patient preferences. While there is some variation in guidelines, such recommendations include the following points [22].

*For small cell lung cancer, 4 cycles of cisplatin and etoposide chemotherapy may be preferred instead of 6 cycles in stages I to III. Replacement of etoposide from intravenous to oral administration can help limit the frequency of hospital visits.

In stage I, surgical resection of the tumor followed by chemotherapy can be considered.

* Radiotherapy with accelerated hyperfractionation 2 times per day can also limit hospital visits.
* For stage IV patients, in selected cases, palliative chemotherapy with platinum and etoposide can be considered along with other supportive care.
* In patients at risk for febrile neutropenia, dose reduction in chemotherapy can be considered with supplemental granulocyte colony-stimulating factor therapy.
* Immune checkpoint inhibitors (durvalumab or atezolizumab) can be omitted, considering the triweekly clinic visits during the maintenance phase.
* In non-small cell lung cancer, for small tumors having stable growth, surgery can be delayed with follow-up chest CT.

Adjuvant chemotherapy can be omitted or stopped early in elderly patients with significant comorbidity, preferably after 3 cycles.

* The cisplatin/docetaxel regimen reduces frequent hospital admission and stays compared to vinorelbine or gemcitabine which require 8 days of administration but have the same efficacy.
* In non-squamous non-small cell lung cancer, the cisplatin and pemetrexed regimen is an efficacious alternative to limit hospital visits.
* For positive epidermal growth factor (EGFR) mutation, oral EGFR-tyrosine kinase inhibitor (TKI) for 1 year on a daily basis is the preferred alternative to adjuvant chemotherapy.
* For small tumors having stable growth, curative radiotherapy can be delayed with follow-up chest CT.

Durvalumab every 4 weeks with a dose of 20 mg/kg-1 is equally efficacious to a dose of 10 mg/kg-1 every 2 weeks, ultimately limiting hospital visits.

* For asymptomatic patients wit [32].

New technologies:

1. The global TERAVOLT consortium was also established in 2020 in response to the COVID-19 pandemic and is a physician-led syndicate focusing on the impact of the pandemic on patients with thoracic malignancies.
2. The report indicates that, on a European level, there is a need for increased data sharing – not only on a country-by-country basis, but also within countries at a regional level. DATA-CAN, the UK's Health Data Research Hub for Cancer, has shown how real-time data can be a vital component of the response to COVID-19 and is currently establishing a Real Time Data Network (RTDN).

3. There is also a role for new technologies such as machine learning to analyse and interpret data collected. Gemelli ART (Advanced Radiation Therapy) of the Agostino Gemelli IRCCS University Hospital Foundation in Italy has developed the GENERATOR Tracer RT protocol, a mobile application that allows the collection and analysis of patient data through an artificial intelligence system, monitoring the health status of these patients as they undergo radiation treatment [32,33].
4. Data such as this would enable services to understand their current demand, identify patients who were no longer accessing services and plan capacity to address the larger than expected number of patients now in the system following the pandemic. The data will also be useful to understand the impact of the pandemic on lung cancer patients' outcomes from the point of diagnosis throughout their treatment journey. However, considerations must be taken to align with national consent and data privacy laws [34-36].

3. RECOMMENDATIONS

In the short term:

Symptom identification: The public and healthcare professionals need better information about how to spot the differences between COVID-19 and lung cancer so that people know which services to access.

Reassurance on safety: Patients need reassuring that services are safe for them to access and so there needs to be investment in COVID-19-free clinical spaces, with appropriate communication about how services are being kept safe.

Public awareness: There needs to be public health information campaigns about lung cancer to raise the public's awareness of the signs and symptoms of lung cancer, and encourage them to seek help if they are concerned about their health.

In the longer term:

Screening and diagnosis: There needs to be investment in strategies to identify lung cancer patients more proactively, such as targeted screening programmes for those people at risk

Robust data: Real time data collection and analysis is needed at a national and local level to identify and address the impact of COVID-19 on lung cancer patients.

Primary care capacity: There needs to be investment in capacity at a primary care level to ensure all patients with suspected lung cancer can be swiftly referred to specialist care [37].

4. FEW CASE STUDY FROM AVAILABLE LITERATURE

4.1 Research by Some Experts

Tertiary Hospital in Madrid say"We annotated 23 lung cancer patients consecutively diagnosed with COVID-19 at our institution (HGUGM; Madrid, Spain) between March 4th, 2020 and May 12th, 2020. Only patients with a confirmatory SARS-CoV-2 RT-PCR were included in the study. And the results is-: All patients had at least 1 COVID-19 related symptom; cough (48%), shortness of breath (48%), fever (39%), and low-grade fever (30%) were the most common. Time from symptoms onset to first positive SARS-CoV-2 PCR was 5.5 days (range 1–17), with 13% of cases needed from a 2nd PCR to confirm diagnosis. There was a high variability on thoracic imaging findings, with multilobar pneumonia as the most commonly found pattern (74%). Main lab test abnormalities were low lymphocytes count (87%), high neutrophil to lymphocyte ratio -NLR- (78%), and elevated inflammatory markers: fibrinogen (91%), c-reactive protein -CRP- (87%), and D-dimer (70%). In our series, hospitalization rate was 74%, 39% of patients developed acute respiratory distress syndrome (ARDS), and the case-fatality rate was 35% (8/23). 87% of patients received anti-viral treatment (87% hydroxychloroquine, 74% lopinavir/ritonavir, 13% azithromycin), 43% corticosteroids, 26% interferon-β, 4% tocilizumab, and 82% of hospitalized patients received anticoagulation. High-oxygen requirements were needed in 39% of patients, but only 1 pt was admitted for invasive MV and was discharged 42 days after admission. Multiple variables related to tumor status, clinical baseline conditions, and inflammation markers were associated with mortality but did not remain statistically significant in a multivariate model. In patients with lung cancer receiving systemic therapy (n = 242) incidence and mortality from COVID-19 were 4.5, and 2.1%, respectively, with no differences found by type of treatment [38].

David Baldwin, Chair, UK Clinical Expert Group for Lung Cancer and Mesothelioma and Report Taskforce member says, "We clinicians are seeing similar late presentations of lung cancer to those that were the norm 20 years ago. With disruptions at an unprecedented level, lung cancer patients simply can't afford to have the clock wound back to where things were. We must redouble our efforts to diagnose

patients early, by urgently restoring awareness and early diagnosis campaigns, rapid diagnostic and treatment pathways and approval of national lung cancer screening programmes. Patients deserve fresh investment and services to make up for lost time and accelerate innovation in lung cancer treatment options."[39].

Arnaud Bernaert, Head of Health and Healthcare at the World Economic Forum said: "Producing and rolling out a COVID-19 vaccine within one year required public-private cooperation on a global scale – it showed what we can do together. This report highlights policy priorities that can be put into place so cancer patients can access the care they need. The pandemic has strained our health and health systems, but there are lessons that can be applied in parallel with treating COVID-19. We hope that the public and private sectors can work together in the year ahead."[40].

Memorial Sloan Kettering Cancer Center (MSKCC) in New York, US examined the course of disease, impact of antitumour treatment and determinants of COVID-19 severity/recovery said:"Severity of COVID-19 is high in lung cancer patients with 62% of patients being hospitalised and 25% who died, but determinants of severity are rather patient-specific, including smoking status and chronic obstructive pulmonary disease (COPD), than tumour-specific characteristics or treatments. Although severe, COVID-19 accounted for a minority of overall lung cancer deaths in the MSKCC during the pandemic (11%),The study population included 102 patients with lung cancer treated at MSKCC who had positive COVID-19 test by RT-PCR between the first case identified on 12 March 2020 through 6 May 2020. Outcomes of interest included dates of hospitalisation, admission to intensive care unit (ICU), intubation and invasive mechanical [41].

4.2 Outcomes of COVID-19 in Patients with Lung Cancer

Methods for treatment -:This is an observational, retrospective, single-center study. We collected all lung cancer patients diagnosed with COVID-19 at Hospital General Universitario Gregorio Marañón, Madrid, Spain between February 24th, 2020 to May 12th, 2020. Patients must have a confirmatory SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) to be included in the study [42]. Clinically suspected cases and cases with close contact to COVID-19 confirmed cases were not included if either not tested or tested negative by RT-PCR. Procedures for real time RT-PCR confirmation of SARS-CoV-2 infection have been described elsewhere [43,44].

Indications of SARS-CoV-2 RT-PCR followed institutional guidelines based on recommendations and case definition available at that moment by the Ministry of Health. Initially, this included only suspicious cases. Suspicious case was any person with a clinical presentation of acute respiratory infection of any severity that causes, among others, fever, cough, or of shortness of breath. Other symptoms such as odynophagia, anosmia, ageusia, muscle pain, diarrhea, chest pain, or headaches, among others, may also be symptoms of suspected SARS-CoV-2 infection according to clinical criteria. We performed SARS-CoV-2 RT-PCR to every suspicious case and included all lung cancer patients attended at our hospital (emergency room, hospitalization, ambulatory office, day care area). [45,46] On March 19th, 2020 an entrance triage was stablished at the Medical Oncology Department consisting on both a questionnaire and temperature control. For either suspicious case or study of close contact, this triage visit was followed by SARS-CoV-2 PCR. In addition, every patient initiating any new cancer therapy was SARS-CoV-2 PCR tested before treatment administration but not subsequently tested if COVID-19 was not clinically suspected [47]. Study of the contacts with confirmed COVID-19 persons corresponded to Public Health and Primary Care Physicians, with no access to this information initially under our registries if the patient was not referred to the hospital for clinical assessment [48].

4.2.1 Outcomes of COVID-19 in patients with lung cancer treated in a Tertiary Hospital in Madrid

Background: Cancer patients represent a vulnerable population for COVID-19 illness. We aimed to analyze outcomes of lung cancer patients affected by COVID-19 in a tertiary hospital of a high-incidence region during the pandemic.

Methods: Researcher annotated 23 lung cancer patients consecutively diagnosed with COVID-19 at our institution (HGUGM; Madrid, Spain) between March 4th, 2020 and May 12th, 2020. Only patients with a confirmatory SARS-CoV-2 RT-PCR were included in the study.

Results: All patients had at least 1 COVID-19 related symptom; cough (48%), shortness of breath (48%), fever (39%), and low-grade fever (30%) [48].

4.2.2 Analysis after applying method and results

Associations between categorical data were tested using Chi-square or Fisher's exact test; Wilcoxon rank sum test or unpaired t test were used for calculations for association with continuous measures. All tests

were conducted at the two-sided 0.05-level with no adjustments for multiple comparisons. We assessed all study variables to analyze correlations with mortality using logistic regression. Correlation between variables was assessed by the Kendall rank correlation method. Correlation plot was drawn with corrplot package. Median confidence intervals were calculated by bootstrapping method with function MedianCI from DescTools package. We conducted receiver-operator characteristic (ROC) curve analysis for NLR. An optimal cut-off to differentiate high-risk versus low-risk groups was determined using the Youden method; sensitivity, specificity, and Youden's index were also reported. All analyses were performed using Prism 8 (version 8.4.3) and R (version 4.0.1).This study was approved by the local Ethics Committee with registration number GOM-HGUGM-2020-04.

5. RESULTS

5.1 Demographic and Clinical Characteristic of Lung Cancer Patients with COVID-19

First SARS-CoV-19 confirmed lung cancer patient in our institution was on March 5th, 2020. Since then a total of 23 more cases were detected as per May 12th, 2020. Daily and cumulative incidence of COVID-19 in lung cancer patients at our institution is comparable to epidemiologic data in Madrid during these 10 weeks (Fig. 1) [49]. Of note, all lung cancer patients included in our series corresponded to suspicious cases and no lung cancer patient was diagnosed of

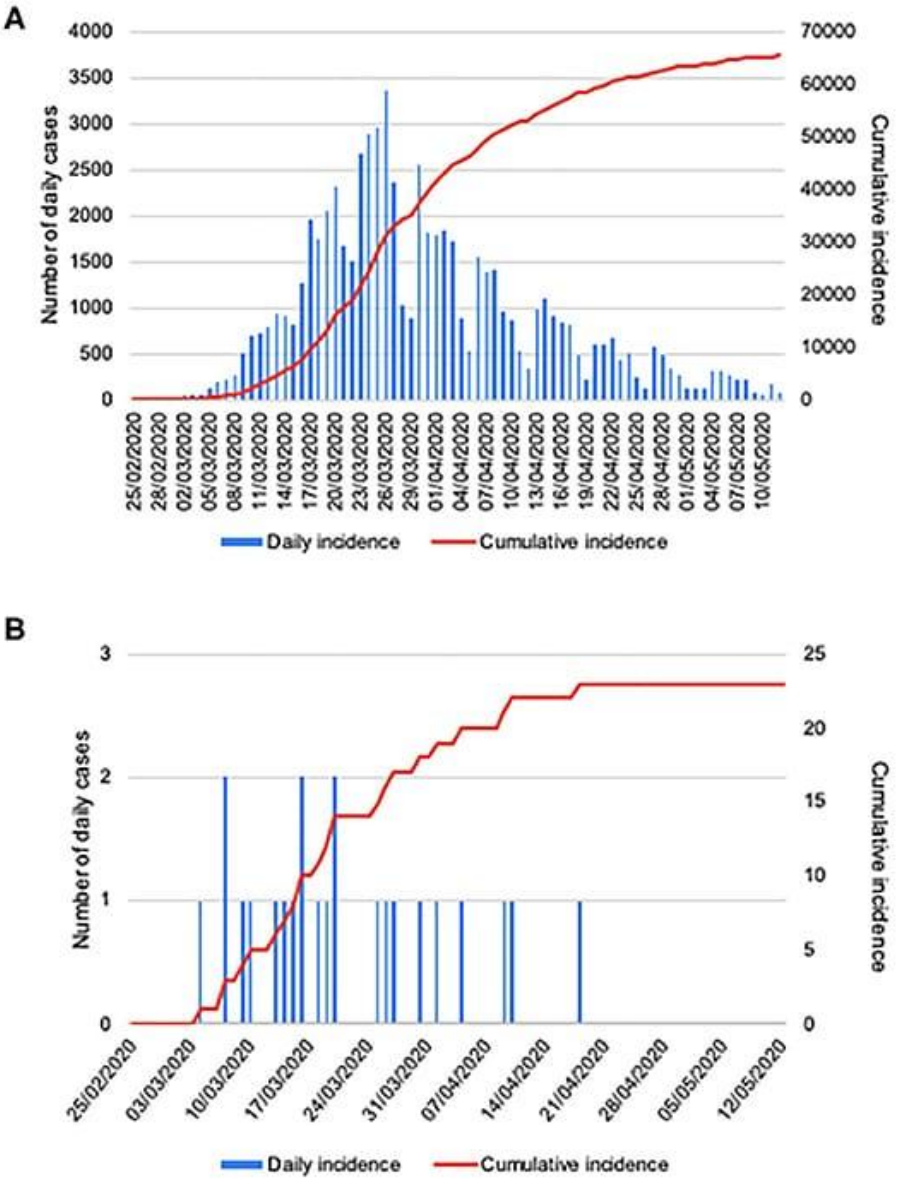

Fig. 1. Daily and cumulative incidence of covid 19 cases

COVID-19 from the upfront triage stablished at the entrance of the Medical Oncology Department [50].

Clinical features of the 23 COVID-19 lung cancer patients resemble average demographics for lung cancer patients (Table 1). Median age was 66 years-old (range 49–86), predominantly male (78%), and past smoking history (87%). Up 87% of patients had at least 1 comorbidity (range 1–7). Most common comorbidities were hypertension (57%), diabetes (39%), and chronic obstructive pulmonary disease—COPD—(30%). Cardiac dysfunction, chronic renal disease, and chronic liver disease were present in 26, 17, and 17%, respectively (Table 1). Two patients (9%) had past tuberculosis infection. Up to 22% of patients had immunosuppressive conditions: 1 patient with HIV infection, 1 patient with liver transplantation under immunosuppressants, 3 patients on chronic steroid intake >10 mg prednisone per day. Only 3 patients were on permanent anticoagulants at the time of COVID-19 diagnosis [12].

6. CONCLUSION

Given the impact of the covid-19 epidemic in the world so far prioritising Lung Cancer after COVID-19 concludes that, while forward progress was temporarily stalled due to the COVID-19 pandemic, coming together to reflect on experiences, barriers, and lessons from delivering lung cancer care during a pandemic offered promise for short-term solutions and future advances in care delivery. Lung cancer patients represent a vulnerable population for COVID-19, according to the high rate of hospitalization, onset of ARDS, and high mortality rate. Although larger series are needed, no differences in mortality were found by type of cancer treatment. Measures to minimize the risk of SARS-CoV-2 infection remain key to protect lung cancer patients.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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