# CASE REPORTS IN THORACIC SURGERY: 2021

EDITED BY: Nuria Maria Novoa
PUBLISHED IN: Frontiers in Surgery

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-83250-536-6
DOI 10.3389/978-2-83250-536-6

## About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

## Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

## Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

## What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

# CASE REPORTS IN THORACIC SURGERY: 2021

Topic Editor:
**Nuria Maria Novoa,** University of Salamanca Health Care Complex, Spain

**Citation:** Novoa, N. M., ed. (2022). Case Reports in Thoracic Surgery: 2021. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83250-536-6

# Table of Contents

frontiers | Frontiers in Surgery

TYPE Editorial
PUBLISHED 04 October 2022
DOI 10.3389/fsurg.2022.1026401



OPEN ACCESS

EDITED BY
Luca Bertolaccini,
European Institute of Oncology (IEO), Italy

REVIEWED BY
Francesco Zaraca,
Ospedale di Bolzano, Italy
Erjia Zhu,
Tongji University, China

*CORRESPONDENCE
Nuria Maria Novoa
nuria.novoa@usal.es

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 23 August 2022
ACCEPTED 16 September 2022
PUBLISHED 04 October 2022

CITATION
Novoa NM (2022) Editorial: Case-reports, a compendium of useful ideas for our daily activity.
Front. Surg. 9:1026401.
doi: 10.3389/fsurg.2022.1026401



# Editorial: Case-reports, a compendium of useful ideas for our daily activity

Nuria Maria Novoa*

Thoracic Surgery Department, University Hospital of Salamanca, Institute of Biomedical Research of Salamanca (IBSAL), Salamanca, Spain

KEYWORDS

case-report, clinical cases, scientific communication, medical literature, peer-review activity

Editorial on the Research Topic
Case-reports, a compendium of useful ideas for our daily activity

Back in the first half of the 20th century and before, case-report and case-report series comprised the most relevant type of manuscripts of the medical literature (1). No doubt that our current medical literature is based on robust scientific methodology making case-reports an outlier to it. However, case-reports fill in a broad area of knowledge difficult to complete with other types of publications. A good clinical case-report focus on an exceptional situation and discuss it with special depth adding a good literature review of the topic. But above all, they present an unusual pathology or circumstance for which no clear or determinant data exists, sometimes raising new hypothesis for research and always full of educational value. They transform an anecdote into evidence. These are important reasons to keep case-report and case-report series as a relevant part of our medical reading (2).

Case-reports are a literature genre and as such, writing a good report has its methodology (3). Authors should always keep in mind the main message posed by the clinical case, why is it noteworthy. This type of paper should be short in length to really focus on the problem including only relevant data and avoiding unnecessary or confusing details. Despite the summary effort, this type of paper is easier to write than most of our current scientific manuscripts. They offer a good opportunity to junior clinicians or researchers to initiate a scientific career.

Peer-reviewed manuscripts offer the warranty of a high-quality publication that adds knowledge to our background. It is true that no causal inference or generalization normally is possible (2). However, it raises doubts and/or new ideas basic for future advances and it offers solutions to difficult problems when dealing with rare disorders, for instance. Although, bias is a great problem as journals tend to publish positive-outcome findings (2), some authors have started performing combined analysis showing the

value of the case-reports compared to clinical studies in complex meta-analysis (4). This new tool opens the door to increase the current value of this type of publication.

In conclusion, I would say that clinical case-reports are still relevant for the medical community. Although, at a certain moment, it was thought they were going to disappear, we are clearly aware they cover a broad area of knowledge not covered by anything else and due to their clear educational value, among others, clinical case-reports will remain an important tool to improvement. Following these ideas, you will find a nice collection of case-reports included in this section that offer new insights to a variety of thoracic surgery problems. From very unusual cases such as the primary pleural squamous cell carcinoma or a bilateral diaphragm rupture to a easy close situation such as the splenic rupture during a VATS lung resection. You will find a group of interesting and well-sorted out clinical cases. I hope they are to your liking and learn from them.

## Author contributions

NMN has contributed to the paper designing the idea, reviewing the literature and writing the manuscript.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## References

1. Nissen T, Wynn R. The history of the case report: a selective review. *JRSM Open*. (2014) 5(4):1–5. doi: 10.1177/2054270414523410

2. Nissen T, Wynn R. The clinical case report: a review of its merits and limitations. *BMC Res Notes*. (2014) 7:264. doi: 10.1186/1756-0500-7-264

3. Guidelines to writing a clinical case report. *Heart Views*. (2017) 18(3):104–5. doi: 10.4103/1995-705X.217857

4. Sampayo-Cordero M, Miguel-Huguet B, Pardo-Mateos A, Moltó-Abad M, Muñoz-Delgado C, Pérez-López J. Agreement between the results of meta-analyses from case reports and from clinical studies regarding the efficacy of laronidase therapy in patients with mucopolysaccharidosis type I who initiated enzyme replacement therapy in adult age: an example of case reports meta-analyses as an useful tool for evidence-based medicine in rare diseases. *Mol Genet Metab*. (2018) 123(2):69–75. doi: 10.1016/j.ymgme.2018.01.002

frontiers in Surgery

CASE REPORT
published: 09 March 2021
doi: 10.3389/fsurg.2021.640089

# Case Report: Surgical Management of Painful Manubriosternal Pseudoarthrosis

*Ronit Bar-Haim*[1]*, *Haim Shtarker*[2,3], *Seema Biswas*[1], *Igor Waksman*[1,3] and *Edward Altman*[1]

[1] Department of Surgery B, Galilee Medical Center, Nahariya, Israel, [2] Department of Orthopedics, Galilee Medical Center, Nahariya, Israel, [3] Faculty of Medicine in Tzfat, Bar Ilan University, Ramat Gan, Israel

A 31-year-old male amateur bodybuilder presented with a 2-year history of chronic pain over the sternum and a clicking sensation in the chest wall on movement. Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) showed no cause for his symptoms. Dynamic ultrasound scan performed at a specialist sports center revealed pseudoarthrosis of the manubriosternal joint (MSJ). After a period of conservative management (rest and analgesia), he failed to improve and underwent debridement and fusion of the MSJ with plates and screws. At follow-up 23 months later, he remains pain-free and has returned to weight lifting and bodybuilding.

**Keywords: manubriosternal joint, pseudoarthrosis, chronic pain, surgery, weightlifter**

OPEN ACCESS

***Edited by:***
*Monica Casiraghi, European Institute of Oncology (IEO), Italy*

***Reviewed by:***
*Paola Ciriaco, San Raffaele Scientific Institute (IRCCS), Italy*
*Mark William Hennon, University at Buffalo, United States*

***Correspondence:**
*Ronit Bar-Haim*
*ronitbarh@gmail.com*

***Specialty section:***
*This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery*

***Received:*** *10 December 2020*
***Accepted:*** *22 January 2021*
***Published:*** *09 March 2021*

***Citation:***
*Bar-Haim R, Shtarker H, Biswas S, Waksman I and Altman E (2021) Case Report: Surgical Management of Painful Manubriosternal Pseudoarthrosis. Front. Surg. 8:640089. doi: 10.3389/fsurg.2021.640089*

## INTRODUCTION

Motor vehicle crashes and chest seat belt restraints are the most common causes of sternal fracture. Reports of sternal injury among sportsmen and athletes are less common, however, with fracture resulting from non-contact trauma described in only sporadic cases in the literature (1–5).

While surgery for sternal fracture after acute trauma is rare, surgical repair of painful chronic non-union after sternal fracture has been described (6), as has surgery for chest pain after poorly healed median sternotomy in cardiac surgery resulting in malunion or pseudoarthrosis (7).

We describe the management of painful manubriosternal joint (MSJ) disruption in an amateur weight lifter and describe the challenge of diagnosis, pitfalls in imaging, and a technique of repair to render the patient symptom-free and able to resume his hobby.

## TECHNIQUE

A 31-year-old man, a bodybuilder, presented with a 2-year history of chronic sternal pain and clicking on movement. On examination, he appeared pain-free and had an athletic body with very well-developed muscles of the torso and upper limbs. On the chest wall, a non-tender, bony thickening was palpable at the MSJ. After repeat consultation and a normal thoracic ultrasound scan, computed tomography (CT) and magnetic resonance imaging (MRI) scans were reported to show no abnormality. The patient's symptoms remained, and after 2-years of repeated consultations (see timeline in **Figure 1**), a dynamic ultrasound scan performed in a specialist sports medical center showed, in the first static phase, in the upright sitting position, a diastasis of 7.5 mm with deformation and elongation of the cartilage of 1.6 cm at the MSJ. The second phase, performed with the patient sitting forward with both arms raised, demonstrated unstable articulation of the manubrium on the body of the sternum with fibrosis of the MSJ—a pseudoarthrosis. Review of the previous MRI scan confirmed the pseudoarthrosis with a visible line of synovial fluid

between the manubrium and the body of the sternum. These findings were consistent with chronic inflammation resulting from weight lifting. After a period of conservative treatment with rest and non-steroidal anti-inflammatory drugs, as there was no improvement, surgery was performed.

Under general anesthesia, a longitudinal midline sternal incision was made. Pathological movement of the MSJ was noted, with proliferation of synovial and fibrotic tissue. All abnormal fibrocartilaginous and synovial tissue was debrided using a high-speed burr. The MSJ was fixated with two 2-inch longitudinal titanium plates, parallel to each other, and three pairs of locked (2.7 cm) and non-locked (2.7 cm) screws to increase stability while permitting initial slight movement with breathing. Autologous bone graft was performed by harvesting cancellous bone from the iliac crest and inserting this into the defect at the MSJ. At the end of the procedure, a stability

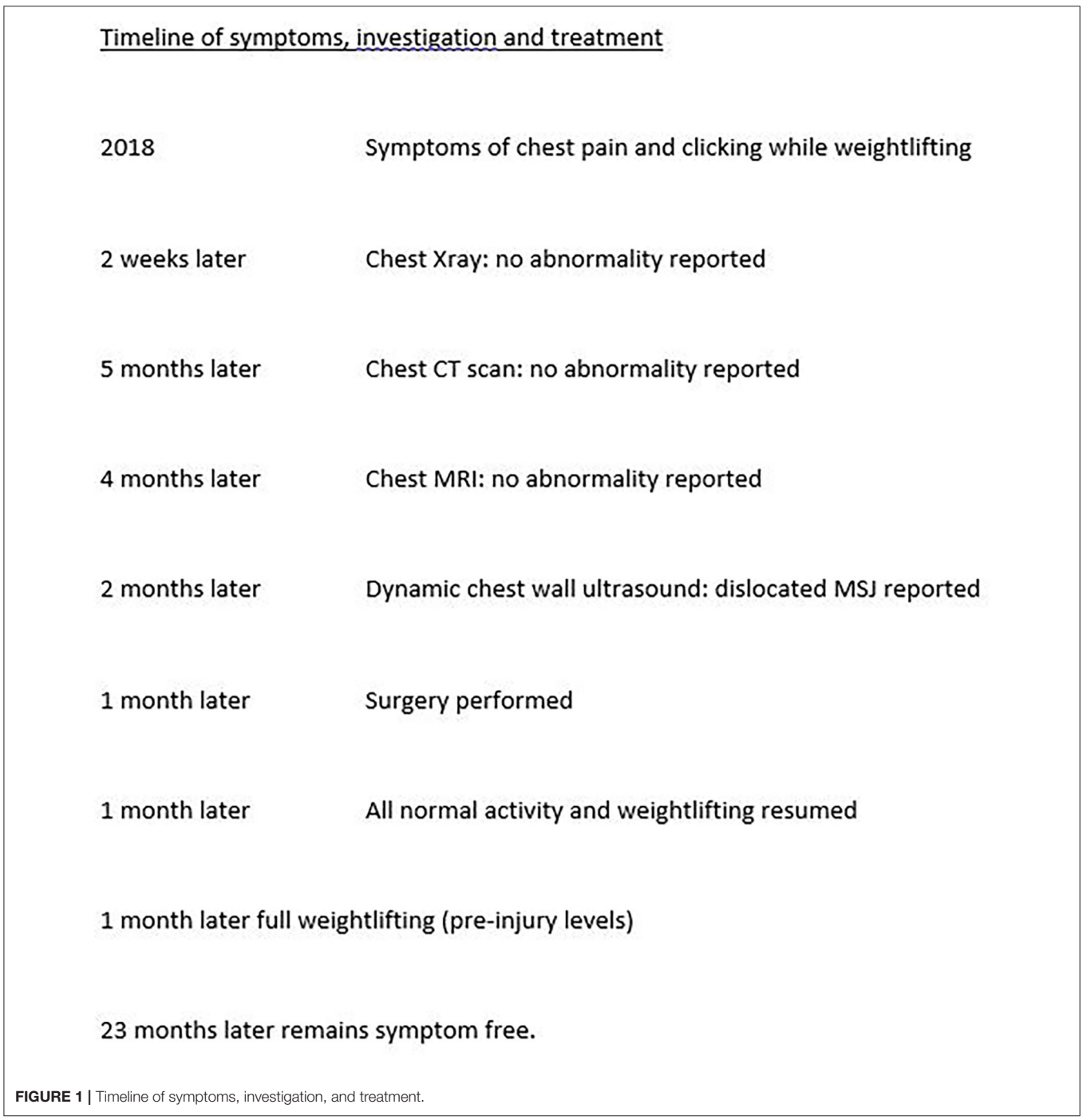


**FIGURE 1 |** Timeline of symptoms, investigation, and treatment.

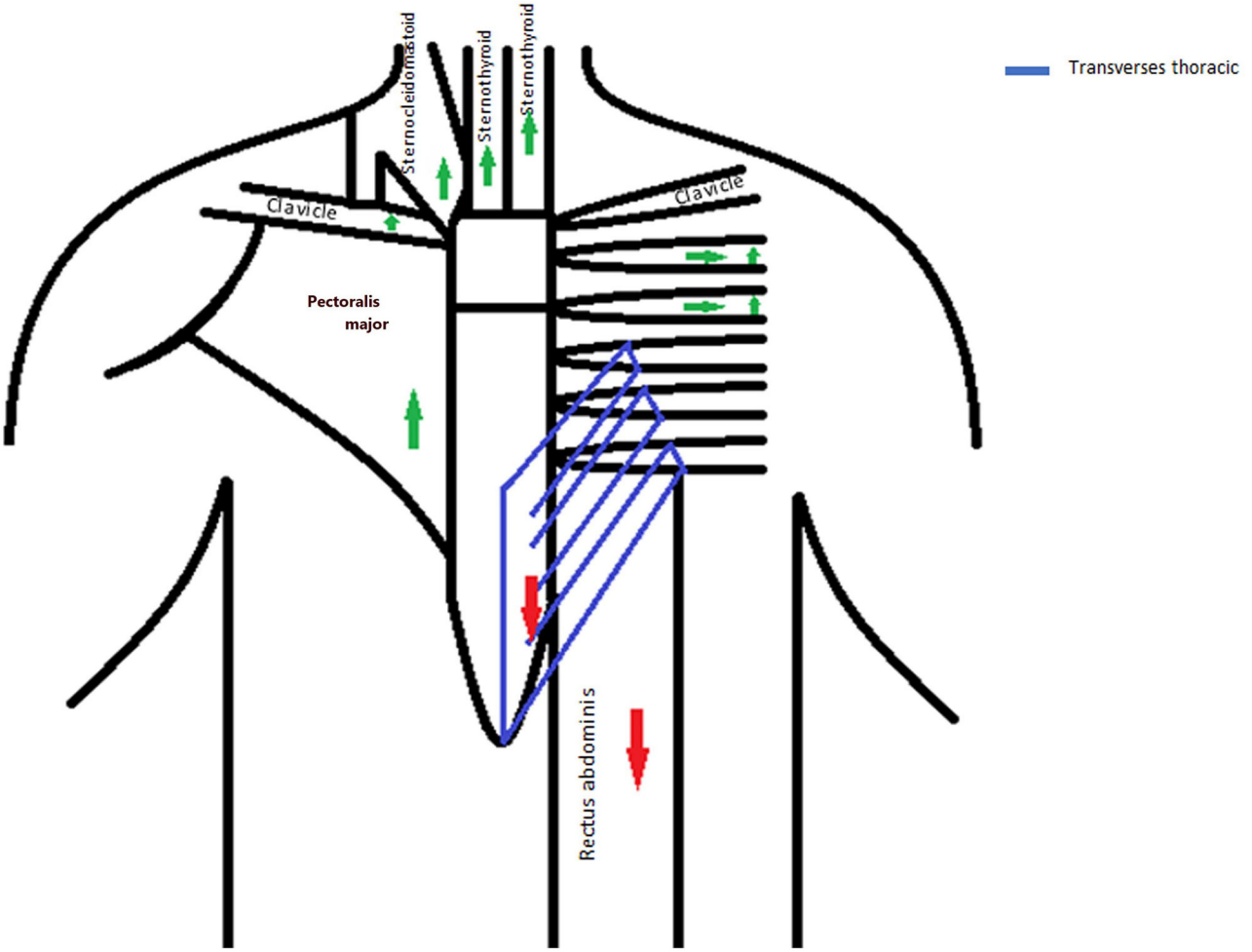


**FIGURE 2 |** Anatomical forces acting on the manubriosternal joint.

check was performed with no pathological movement of the MSJ. The patient made an uneventful postoperative recovery and was discharged 7 days later after completion of a course of physical therapy. He was pain-free and without any limitation of movement. He returned to normal activities 2 weeks later. After 1 month, he was regularly lifting weights at preinjury levels. At 23 month follow-up, the patient remains pain-free and has returned to regular exercise and weight lifting.

## COMMENT

While much has been written about the management of sternal fractures after blunt trauma and non-union after median sternotomy for cardiac surgery, guidance on the management of MSJ pseudoarthrosis remains relatively scarce.

The first challenge is in understanding the pathology in the absence of a single traumatic incident:

There are two known mechanisms of MSJ dislocation or disruption; both entail the high-energy trauma expected in a motor vehicle crash. The first type of injury results from direct impact with posterior displacement of the body of the sternum. The second and more common injury type follows flexion–compression trauma of the thorax and neck where the neck is forcefully hyperflexed while the chin, clavicles, or ribs displace the manubrium posteriorly.

In the absence of a single incidence of major trauma, a careful history of how and when the pain started is important: the mechanism here is repeated low-level trauma or stress on the chest wall. A key feature of the symptoms is clicking of the fibrocartilaginous pseudoarthrosis on movement of the unstable MSJ [also reported by (4), in a rugby player complaining of chest pain over 2-years].

The strength and stability of the MSJ rely on the attachment of the clavicles and first rib to the body of the manubrium and the strong ligamentous attachments of the second ribs to the MSJ. These attachments result in a non-mobile joint. In our patient, years of bodybuilding and weight lifting resulted in these muscles and ligaments stretched repeatedly under considerable force in opposite directions. Cranial stretching involved the attachment of the manubrium to the spine

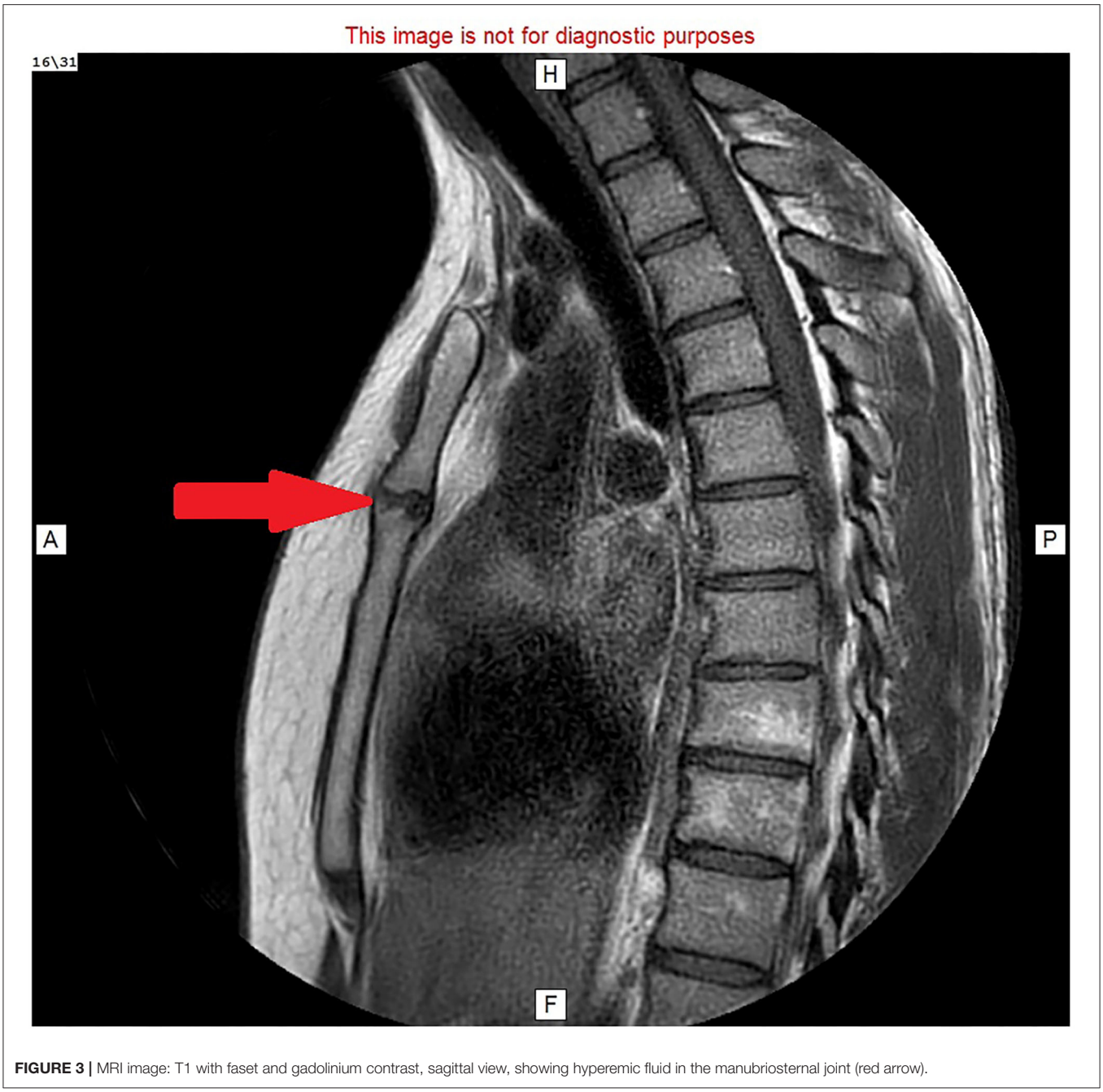


**FIGURE 3 |** MRI image: T1 with faset and gadolinium contrast, sagittal view, showing hyperemic fluid in the manubriosternal joint (red arrow).

through the first and second ribs and the attachment to the shoulders through the clavicles, the sternal head of the sternocleidomastoid and part of the pectoralis major attached anteriorly to the manubrium and sternum, and the sternohyoid and sternothyroid muscles attached posteriorly to the manubrium. Caudally, stretching in the opposite direction involved the transverse thoracis muscle attached to the posterior surface of the body of the sternum and the strong rectus abdominis attached to the distal part of the sternum (**Figure 2**). Repetitive injury resulted in pseudoarthrosis of the MSJ.

Bilateral first rib fractures and pseudoarthrosis and callus formation at the thoracic inlet were described by Satija et al. (5) in a 17-year-old boy who complained of pain after 18 months of regular weight lifting. Zabaleta et al. (4) describe sternal pseudoarthrosis in a rugby player who similarly underwent debridement and titanium osteosynthesis.

Rarer still are reported non-traumatic inflammatory lesions of the manubriosternal synchondrosis reported among athletes complaining of chronic post-exercise pain at the MSJ (2). While clinical practice in high-energy chest trauma is focused on thorough investigation to

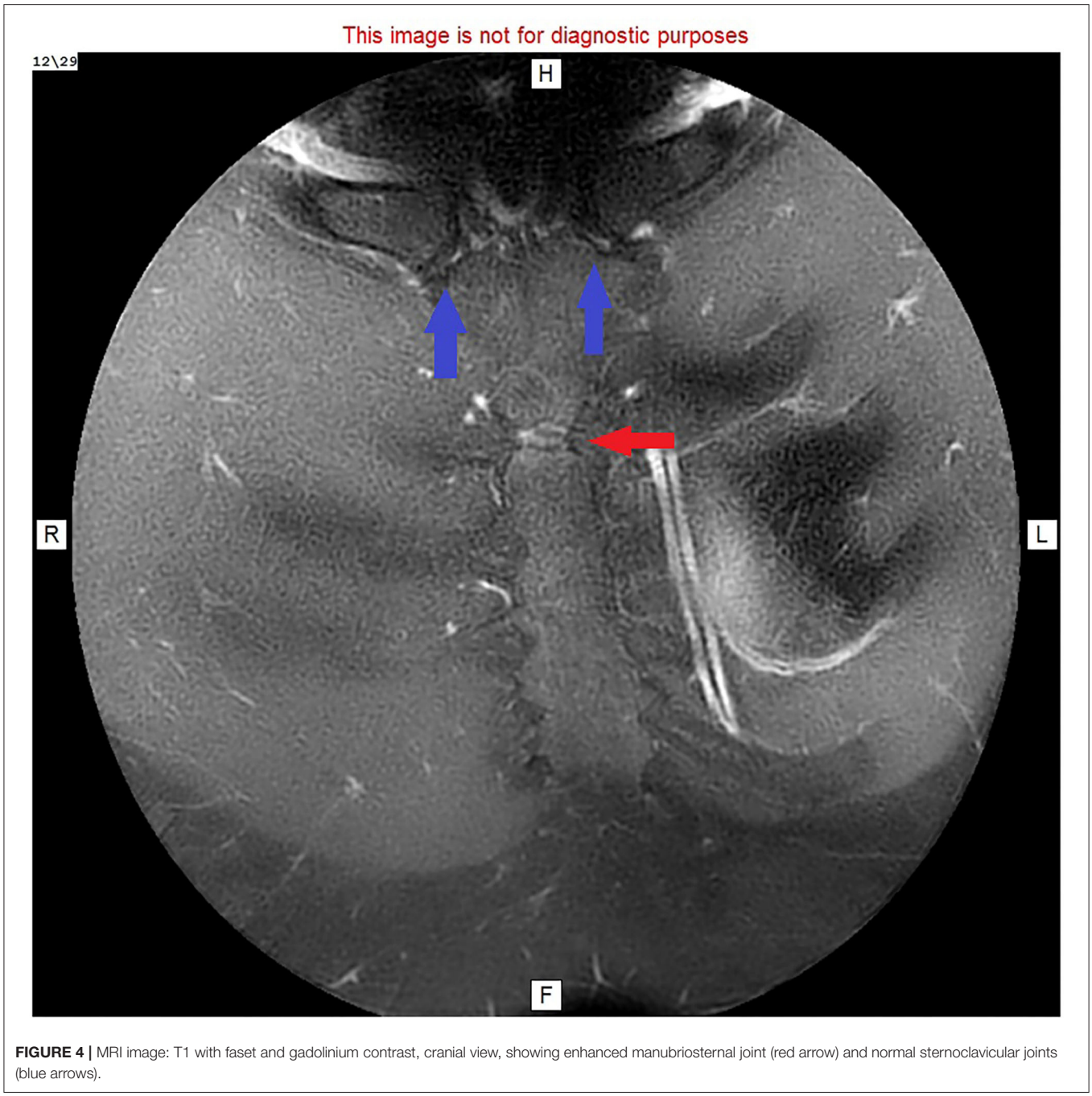


**FIGURE 4 |** MRI image: T1 with faset and gadolinium contrast, cranial view, showing enhanced manubriosternal joint (red arrow) and normal sternoclavicular joints (blue arrows).

detect internal chest complications leading to cardiac, pulmonary, or vascular compromise, our emphasis is on the difficulty of diagnosis of chest wall complications resulting from relatively low-energy trauma. Dynamic testing was crucial in reaching the diagnosis. Thus, the second challenge was reaching the correct diagnosis through appropriate imaging:

Imaging findings of MSJ dislocation have been described (3), but pseudoarthrosis of the MSJ is rarely described in the literature. Interpretation of MRI scans without careful attention to the patient's history presents a challenge (**Figures 3**, **4**). The key to diagnosis is functional or dynamic imaging, recreating the patient's symptoms while imaging the abnormal movement or articulation of the MSJ.

The final challenge was in selecting an appropriate operative technique to render the patient pain-free with a fused stable MSJ able to withstand the resumption of sporting activity:

While most sternal injuries are managed conservatively, there are three key indications for surgery: (I) the presence of a sternal deformity, (II) loss of sternal continuity for a period of more

than 6 weeks, and (III) persistence of chest pain for 2–8 weeks after trauma.

Surgical fixation of the dislocated MSJ using plates and screws has yielded demonstrably better results than that achieved with wire fixation (8). The superficial positioning of the sternum beneath the chest wall skin limits the thickness of plates that can be used; thus, thin plates are used. Parallel positioning of the plates, with both locked and non-locked screw fixation, further increases stability while permitting initial movement with breathing. We recommend the use of two plates for two reasons: to limit movement (to prevent rotational motion between the manubrium and sternum) and to maintain the strength of the fixation. The use of locked screws makes for a more rigid fixation, especially in thin bone—an important consideration in treating pseudoarthrosis. To date, we have not experienced complications, including infection, using chest wall plate and screw fixation after primary surgery, albeit a relatively rare procedure in our department. Seroma and infection have been reported after rib fixation, with infection rates in small series as high as 7% (9). Infection is the key disadvantage of plate and screw fixation, but the stable fixation this gives surpasses pin or wire fixation—also potentially complicated by infection.

Twenty-three months after surgery, the patient reports no further clicking or pain, and, on examination, there is no further evidence of movement at the MSJ.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they are stored in confidential patient medical records. Requests to access the datasets should be directed to ronitbarh@gmail.com.

## ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## REFERENCES


1. Alent J, Narducci DM, Moran B, Coris E. Sternal injuries in sport: a review of the literature. *Sports Med*. (2018) 48:2715–24. doi: 10.1007/s40279-018-0990-5
2. Kell R, Ole K, Lene V. Manubrium sterni stress fracture: an unusual complication of non-contact sport. *Br J Sports Med*. (1996) 30:176–7. doi: 10.1136/bjsm.30.2.176
3. Baker JC, Demertzis JL. Manubrial stress fractures diagnosed on MRI: report of two cases and review of the literature. *Skeletal Radiol*. (2016) 45:833–7. doi: 10.1007/s00256-016-2357-z
4. Zabaleta J, Aguinagalde B, Fuentes MG, Bazterargui N, Izquierdo JM. El jugador de rugby con una "pata de elefante" en el pecho [Rugby player with an "elephant's foot" in the chest]. *Cir Esp*. (2013) 91:342–4. doi: 10.1016/j.ciresp.2011.11.009
5. Satija L, Debnath J, George RA, Ghai SK, Gill BS. Bilateral first rib fractures with pseudoarthrosis in a weight lifter. *Med J Armed Forces India*. (2011) 67:184–6. doi: 10.1016/S0377-1237(11)60032-4
6. Gallo DR, Lett ED, Conner WC. Surgical repair of a chronic traumatic sternal fracture. *Ann Thorac Surg*. (2006) 81:726–8. doi: 10.1016/j.athoracsur.2004.11.057
7. Goy JJ, Poncioni L, Morin D. Chest pain due to severe sternal pseudoarthrosis post-coronary artery bypass surgery. *Circulation*. (2010) 122:1134–5. doi: 10.1161/CIRCULATIONAHA.109.898940
8. Voss B, Bauernschmitt R, Will A, Krane M, Kröss R, Brockmann G, et al. Sternal reconstruction with titanium plates in complicated sternal dehiscence. *Eur J Cardiothorac Surg*. (2008) 34:139–45. doi: 10.1016/j.ejcts.2008.03.030
9. Chepla KJ, Selgado CJ, Tang CJ, Mardini S, Evans KK. Late complications of chest wall reconstruction: management of painful sternal nonunion. *Semin Plast Surg*. (2011) 1:98–106. doi: 10.1055/s-0031-1275176


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Surgery

CASE REPORT
published: 21 May 2021
doi: 10.3389/fsurg.2021.679757

# Case Report: COVID-19 Pneumonia Following Left Pneumonectomy for Lung Cancer Complicated by Empyema and Bronchopleural Fistula

*Alberto Testori*[1]*, *Veronica M. Giudici*[2], *Marco Alloisio*[2] and *Ugo Cioffi*[3]

[1] Department of General and Thoracic Surgery, IRCCS Humanitas Research Hospital, Milan, Italy, [2] Department of General and Thoracic Surgery, Humanitas University, Milan, Italy, [3] Department of Surgery, University of Milan, Milan, Italy

**Background:** Venous and arterial thromboembolism is commonly reported in critically ill COVID-19 patients, although there are still no definitive statistical data regarding its incidence.

**Case presentation:** we report a case of a patient who fell ill with Covid during hospitalization for a pneumonectomy complicated by empyema and bronchopleural fistula. The patient, despite being cured of COVID, died after 14 days for pulmonary thromboembolism.

**Conclusion:** Our case strengthens the suggestion of adequate thromboprophylaxis in all hospitalized COVID patients and of increasing prophylaxis in critically ill patients even in the absence of randomized studies

**Keywords: COVID-19 pneumonia, pneumonectomy, thromboembolism, thromboprophylaxis, bronchopleural fistula, empyema**

OPEN ACCESS

***Edited by:***
*Paola Ciriaco, San Raffaele Scientific Institute (IRCCS), Italy*

***Reviewed by:***
*Piergiorgio Muriana, San Raffaele Scientific Institute (IRCCS), Italy*
*Alessandro Bandiera, San Raffaele Hospital (IRCCS), Italy*
*Carmelina Cristina Zirafa, University Hospital of Pisa, Italy*

***Correspondence:**
*Alberto Testori*
*alberto.testori@humanitas.it*

***Specialty section:***
*This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery*

***Received:*** *12 March 2021*
***Accepted:*** *16 April 2021*
***Published:*** *21 May 2021*

***Citation:***
*Testori A, Giudici VM, Alloisio M and Cioffi U (2021) Case Report: COVID-19 Pneumonia Following Left Pneumonectomy for Lung Cancer Complicated by Empyema and Bronchopleural Fistula. Front. Surg. 8:679757. doi: 10.3389/fsurg.2021.679757*

## INTRODUCTION

Patients with COVID-19 pneumonia exhibit a range of abnormal coagulation parameters resulting in increased mortality rate. Alterations of the hemostatic system include increased D-dimer and fibrin degradation products, changes in activated partial thromboplastin time (aPTT), and prothrombin time international normalized ratio (INR).

COVID-19 can predispose to venous and arterial thromboembolic disease as a result of excessive inflammation, hypoxia, immobilization and diffuse intravascular coagulation (1). Exact knowledge of the incidence of thrombotic complications in COVID-19 patients is important for decision making regarding the intensity of thromboprophylaxis, especially in ICU patients who are at higher risk for thrombosis.

Here, we report a case of a patient who fell ill with Covid during hospitalization for a pneumonectomy. The patient, despite being cured of COVID, later died of probable pulmonary thromboembolism.

## CASE PRESENTATION

A 78-year-old man, who previously underwent to a radical cystectomy, was diagnosed of a left lung mass during a follow up with chest X-ray. A chest-CT, a PET-CT scan (**Figure 1**) and a CT guided fine needle aspiration biopsy revealed the presence of a 7-cm lung Adenocarcinoma, with no lymph nodal involvement and/or metastasis.

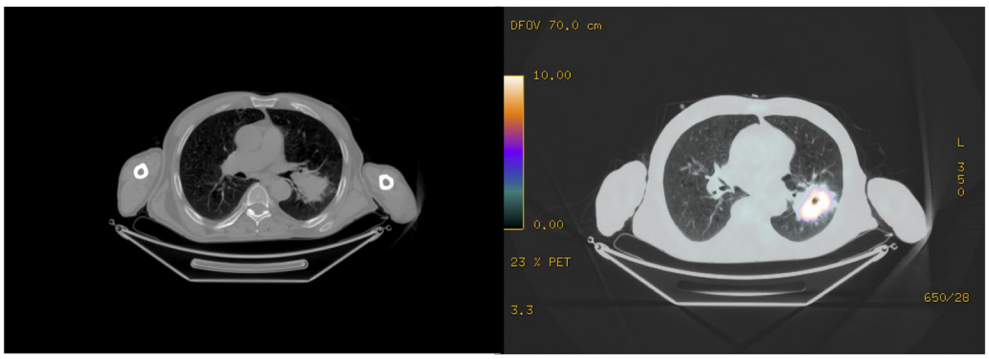


**FIGURE 1 |** A PET-CT scan revealing the presence of a 7-cm left lung neoformation with no nodal involvement.

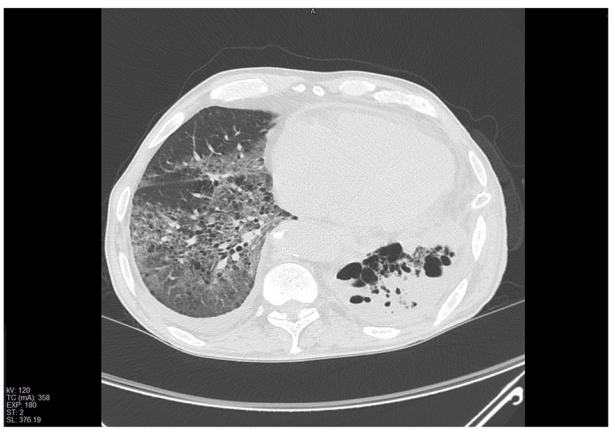

**FIGURE 2 |** Chest CT-scan showing the presence of extensive pulmonary infarction in the residual parenchyma.

So, the patient underwent to a lower left lobectomy surgery and a typical lingulectomy in anterolateral thoracotomy. Given the increase in inflammation indices and the progressive increase in opacity of the residual left lung parenchyma due to infarction (**Figure 2**), the patient was submitted to a left pneumonectomy. The hospital stay lasted 10 days and the patient was discharged in good clinical conditions. The final histopathological diagnosis was a 7,5-cm lung Adenocarcinoma; the bronchial surgical margin was negative and visceral pleural invasion was not observed. Of the 12 dissected lymph nodes, all were reported as negative and the pathological stage was reported as IIIA (T4N0M0).

Four days later, he was readmitted to the ward due to fever and subcutaneous emphysema. A chest CT scan was performed, it showed the presence of a left abundant pleural effusion. A chest tube drainage was placed, an Enterococcus faecium was isolated from pleural fluid a therapy with linezolid 600 mg/twice a day intravenously was set. A 4-mm bronchopleural fistula was diagnosed with a flexible bronchoscopy (**Figure 3**) and the patient underwent to endoscopic lipofilling treatment (2). A nasopharyngeal COVID swab was performed and resulted positively, the patient was immediately transferred in COVID-ward.

The patient developed dyspnoea, chest tightness and wheezing. Two days later, due to the worsening of clinical conditions he underwent to a chest CT-scan in which almost all of the right lung had a non-homogeneous increase in density, with diffuse ground glass opacity (GGO) and consolidations (**Figure 4**). With nasal oxygen, SpO2 was between 85 and 90%, so Venturi mask was introduced with 60% of FO2. His level of LDH was 321 and of D-Dimer 1,785 ng/ml. Remdesivir associated with steroids were introduced, antibiotic therapy was updated introducing meropenem 3 gr once a day intravenously.

After a successful 14-day period of treatment with a constant improvement of respiratory conditions, a new nasopharyngeal swab was performed and resulted negatively. White blood cell and lymphocyte counts were normal, the C-reactive protein levels continued to regress, there was no important biochemical abnormality (LDH 208 and D-Dimer 645), with nasal oxygen 2l, SpO2 was between 97 and 100%. The patient underwent to a new chest CT-scan, with an almost complete recovery (**Figure 5**). The patient was transferred in a dedicated ward of ex-COVID, and he was scheduled for a new procedure of lipofilling in bronchoscopy.

Following an increase in inflammation parameters, a new sample of pleural fluid was taken from the thoracic drainage, with isolation of Pseudomonas aeruginosa and Candida albicans and a new antibiotic therapy was setting with levofloxacin 500 mg, once a day and piperacillin/tazobactam 4,5 g/3 times a day. Death occurred 14 days later due to cardio-circulatory arrest refractory to resuscitation maneuvers. The autopsy was not done because the relatives did not give consent and also because the echocardiogram performed during the resuscitation maneuvers showed that the patient suffered from massive intracardiac coagulation.

## DISCUSSION

During COVID-19 pandemic, like previously described in China, we faced a reduction or even a suspension of elective surgery,

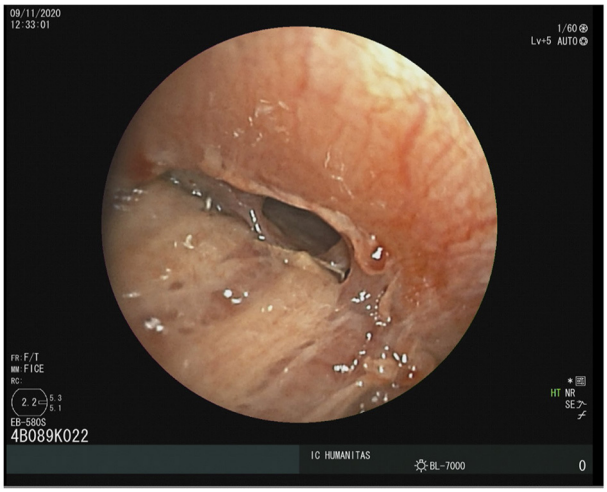


**FIGURE 3 |** A flexible bronchoscopy showing a 4-mm bronchopleural fistula.

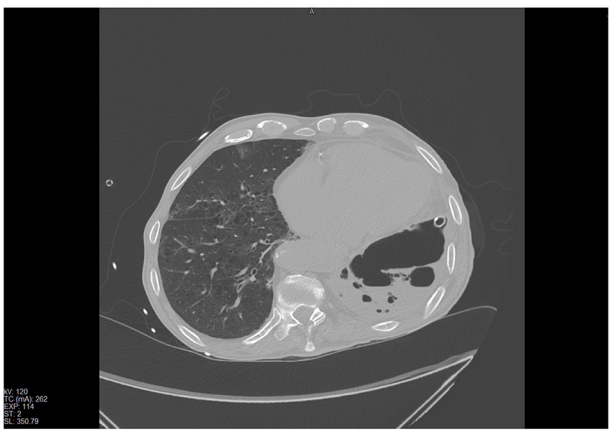

**FIGURE 4 |** Chest CT scan revealing a non-homogeneous increase in density, diffuse GGO and consolidations at the right lung.

due to the reduction of the availability of hospital beds, especially in intensive-care units (ICUs), and an increasing number of infections between health people (2). Is stated, also, that COVID-19 that develops in perioperative time is a risk factor for increased length of stay, morbidity and mortality, especially in thoracic surgery, were the lung, is manipulated to perform parenchymal resection (3, 4).

Various studies worldwide stated that hospitalized, ill coronavirus disease 2019 (COVID-19) patients are frequently developing laboratory abnormalities compatible with a state of hypercoagulability and clinically a high prevalence of thromboembolic events (5). Ranucci et al. (1) recently reported a coagulation analyses including d-dimers, fibrinogen levels, in the COVID-19 patients, and reported the procoagulant profile on ICU admission with median d-dimer levels 10 times the upper limit of normal (5.5 mg/L).

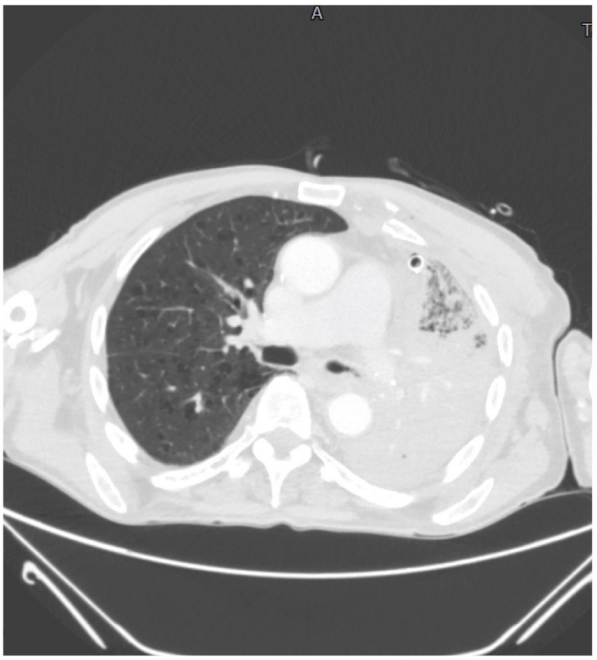


**FIGURE 5 |** An almost complete recovery revealed by a new chest CT scan.

Although the number of postmortem pathologic reports are limited, vascular wall thickening, stenosis of the vascular lumen, and microthrombus formation accompanying the findings of ARDS have been reported by Luo et al. (6).

Hypercoagulation has also been described in the systemic circulation, have been described thrombosis and major thromboembolic sequelae including Pulmonary Embolism in 20–30% of ICU patients due to hypercoagulability with hyperfibrinogenemia (7, 8).

The effect of heparin, mainly LMW heparin, is reported by Tang et al. (9) showing reduced mortality in cases with coagulopathy treated with heparin compared to patients who had coagulopathy not treated with heparin (40.0 vs. 64, 2%, respectively; $p = 0.029$). Heparin exhibits anti-inflammatory effects by neutralizing DAMPs to protect endothelial cells and reduce pulmonary edema and vascular loss.

In the clinical case we treated, the patient was subjected to a prophylactic low-molecular-weight heparin therapy, already before contracting COVID.

The heparin dosage for patients undergoing oncological thoracic surgery is established according to the Caprini score. This score is based on several factors including age, weight, a history of thromboembolism, prolonged immobilization. According to the Caprini Score, our oncological patients, who are undergoing surgery, receive low molecular weight subcutaneous heparin at a dosage of 0.3 ml, 2,850 Ul the night before surgery until 2 days after. From the third postoperative day, the dosage is increased to 0.4 ml, 3,800 Ul or 0.6 ml, 5,700 Ul for up to 25 days after surgery or until complete mobilization.

However, the question at this point is: is this dosage enough for oncological patients who contract COVID?

For oncological patients, who already have an increased thrombotic risk, it would be better to consider an increase in the heparin dosage (10). Therefore, not only for prophylactic but also for anticoagulant purposes.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because case report. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## ACKNOWLEDGMENTS

We thank Dr. Gerardo Cioffi, native speaker, for reviewing the English language.

## REFERENCES

1. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, et al. The procoagulant pattern of patients with Covid-19 acute respiratory distress syndrome. *J Thromb Haemost.* (2020) 18:1747–51. doi: 10.1111/jth.14854
2. Bottoni E, Banzatti BP, Novellis P, Ferraroli GM, Alloisio M. Endoscopic lipofilling for the treatment of bronchopleural fistulas after anatomic lung resection. *Ann Thorac Surg.* (2021) 111:e143–5. doi: 10.1016/j.athoracsur.2020.05.123
3. Testori A, Cioffi U, Ciulla M, Bottoni E, Cariboni U, Perroni G, et al. Surgery at the frontline at the time of the COVID-19 outbreak. *Thorac Cancer.* (2020) 11:3057–9. doi: 10.1111/1759-7714.13666
4. Tian S, Hu W, Niu L, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol.* (2020) 15:700–4. doi: 10.1016/j.jtho.2020.02.010
5. Testori A, Perroni G, Voulaz E, Crepaldi A, Alloisio M. Pulmonary lobectomy after COVID-19. *Ann Thorac Surg.* (2021) 111:e181–2. doi: 10.1016/j.athoracsur.2020.08.004
6. Danzi GB, Loffi M, Galeazzi G, Gherbbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J.* (2020) 41:1858. doi: 10.1093/eurheartj/ehaa254
7. Luo W, Yu H, Gou J, Li X, Sun Y, Li J, et al. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). *Preprints.* (2020) 2020:2020020407. doi: 10.1097/TP.0000000000003412
8. Lok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* (2020) 191:145–7. doi: 10.1016/j.thromres.2020.04.013
9. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* (2020) 18:1094–9. doi: 10.1111/jth.14817
10. Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, et al. Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. *Circulation.* (2020) 142:184–6. doi: 10.1161/CIRCULATIONAHA.120.047430

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Surgery

CASE REPORT
published: 18 June 2021
doi: 10.3389/fsurg.2021.688236

# An Unusual Histology for a Lung Nodule: A Case Report of Primary Pulmonary Paraganglioma

*Alessandra Mazzucco[1]*, Eleonora Poirè[1], Andrea Leporati[1], Matteo Chiari[1], Laura Moneghini[2], Giorgio Ghilardi[1] and Alessandro Baisi[1]*

[1] Thoracic Surgery Unit, University of Milan—Aziende Socio Sanitarie Territoriali (ASST) Santi Paolo e Carlo, Milan, Italy, [2] Unit of Anatomical Pathology—Aziende Socio Sanitarie Territoriali (ASST) Santi Paolo e Carlo, Milan, Italy

**Introduction:** Primary pulmonary paraganglioma is a rare tumor with few cases reported in literature and unspecific clinical presentation.

**Case Presentation:** A 49-year-old woman presented to our department with an incidental finding of a pulmonary mass at chest X-ray and no associated clinical symptom. The CT scan and the FDG-PET showed mild uptake of contrast, but a definitive diagnosis was only possible after surgery through histopathological examination.

**Conclusion:** Paragangliomas originating in the pulmonary tissue are generally non-functioning masses discovered incidentally in otherwise asymptomatic patients. Surgery appears to be the best treatment option, with only radiologic follow-up necessary afterwards.

**Keywords: paraganglioma, thoracic surgery, VATS, lung nodule, rare tumor, case report**

OPEN ACCESS

***Edited by:***
*Nuria Maria Novoa, University of Salamanca Health Care Complex, Spain*

***Reviewed by:***
*Savvas Lampridis, 424 General Military Hospital, Greece*
*Cecilia Pompili, University of Leeds, United Kingdom*

****Correspondence:***
*Alessandra Mazzucco*
*alessandra.mazzucco@hotmail.it*

***Specialty section:***
*This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery*

***Received:*** *30 March 2021*
***Accepted:*** *27 May 2021*
***Published:*** *18 June 2021*

***Citation:***
*Mazzucco A, Poirè E, Leporati A, Chiari M, Moneghini L, Ghilardi G and Baisi A (2021) An Unusual Histology for a Lung Nodule: A Case Report of Primary Pulmonary Paraganglioma. Front. Surg. 8:688236. doi: 10.3389/fsurg.2021.688236*

## INTRODUCTION

Primary pulmonary paragangliomas are rare neuroendocrine tumors with few cases reported in the literature. Generally, affected patients show no symptoms and usually discover the mass incidentally during unrelated medical examinations. We report a case of primary pulmonary paraganglioma in an asymptomatic 49-year-old woman.

## CASE PRESENTATION

A 49-year-old Caucasian woman, an active smoker (15 packs/year) with an otherwise silent past medical history, presented with a dry cough that worsened in the supine position. While the cough resolved with proton-pump inhibitor (PPI) therapy, suggesting a gastrointestinal nature of the symptom, the patient also underwent a routine chest radiograph. The imaging showed a nodule with a diameter of 3.5 cm in the right lower lobe. Thus, a chest CT scan was performed, which confirmed the presence of a solid lesion with well-defined margins, mild contrast enhancement, and a diameter of 34 × 26 mm in the anterior basal segment of the inferior right pulmonary lobe. The exam also revealed an enlarged axillary lymph node that was later confirmed to be inflammatory in nature. To further characterize the lesion, a PET-CT scan with an injection of 18F-fluorodeoxyglucose (FDG) was done; the images showed mild uptake at the level of the nodule in the right lower lobe (with a maximum SUV of 2.8) (**Figures 1**, **2**), suggesting a possibly benign or locally invasive biological behavior. Fine-needle biopsy for typing of the lesion was attempted but ultimately not performed due to poor compliance of the patient

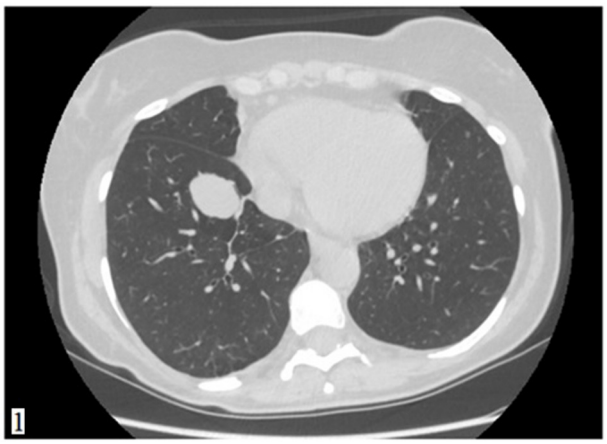

**FIGURE 1 |** A CT scan showing a solid lesion with well-defined margins in the anterior segment of the inferior lobe of the right lung.

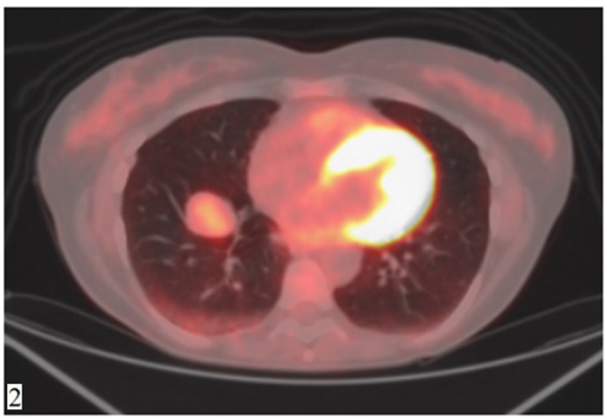

**FIGURE 2 |** FDG-PET showing mild contrast uptake at the level of the nodule (SUV max 2.8).

during the CT-guided procedure. Therefore, wedge resection of the right inferior lobe and nodal sampling were performed with video-assisted thoracoscopic surgery. A frozen section procedure was performed during the operation, which gave unconclusive results. Hence, it was decided not to perform a completion lobectomy but to wait for the final histological results. The tissue specimen analyzed at histology showed richly vascularized intrapulmonary solid proliferation (**Figure 3A**) that comprised two types of cells: epitheliomorphic and spindle-shaped cells. The former type of cells had large eosinophilic cytoplasm and moderately atypical nuclei (nucleolates) partially dispersed in a loose stroma crossed by ill-defined septa (**Figure 3B**); the latter cells, also called "sub-tentacular cells," were interposed with moderate infiltrate of lympho-plasma cells (**Figure 3C**). No necrosis was found in the sections examined, and the mitotic index was <1 mitosis for 10 high-magnification fields (10 HPF, 40X). At immunocytochemistry, all cellular elements showed a strong positive reaction for synaptophysin (Syn) and neuron-specific enolase (**Figure 3D**), while there were only areas of positivity to the S-100 protein in correspondence of the sub-tentacular elements. The dissected lymph nodes were negative. The final diagnosis was a primary pulmonary paraganglioma. The postoperative course was uneventful, with the thoracic drainage removed on the third postoperative day (POD) and no signs of pneumothorax on the chest radiograph performed afterward. The patient was discharged from the hospital on the fourth POD. At the latest checkup, 1 month after the hospital discharge, she showed no sign of relapse on the chest radiograph. After multidisciplinary discussion with the Oncology, Radiology, and Pneumology Departments, it was decided to proceed with radiologic follow-up at 3-month intervals for the first semester with a chest CT scan, then in 6 months for the following year, and later maintain a 1-year radiologic follow-up either with chest radiographs or a CT scan. The main limitation on deciding the timing of the follow-up was the scarcity of available literature on both the treatment and the recurrence rates; however, the available reports seem to suggest an indolent nature of this tumor with an unlikely tendency to recur, which is what informed about our decision on not performing completion of a lobectomy.

## DISCUSSION

Paragangliomas are rare neuroendocrine tumors that arise from the chromaffin cells of the extra-adrenal autonomic paraganglia (1). Their incidence is largely unknown, as they tend to be described in the literature mostly in association with pheochromocytomas; however, the incidence of these tumors combined has been estimated to be about two to eight cases/million a year (2, 3).

Most paragangliomas appear to be sporadic (4), with the majority of patients affected being females and middle-aged (5). Paragangliomas can be associated with either sympathetic or parasympathetic cells; the former are usually "functioning tumors," as they secrete catecholamines, while the latter have a tendency to be "non-functioning." Catecholamine-secreting paragangliomas often present with symptoms similar to those of pheochromocytomas (1) (i.e., diaphoresis, headache, and hypertension), whereas non-functioning tumors are silent and are discovered incidentally.

Extra-adrenal paragangliomas are more commonly silent, and if they do present symptoms, these are mostly related to the mass effect at the site of the tumor. Primary pulmonary paragangliomas are rare even among the extra-adrenal paragangliomas, with <30 cases reported in literature (5). The majority of reported patients were asymptomatic and had a nodule discovered during imaging studies of the chest (6). In a minority of cases, there were symptoms consistent with the localization of the mass, such as cough or chest pain (5).

The differential diagnosis of primary pulmonary paraganglioma should include many different conditions, including pulmonary carcinoma, pulmonary tuberculosis, pulmonary mycosis, either round or organizing pneumonia, inflammatory pseudo-tumors, and metastatic lung cancer (5).

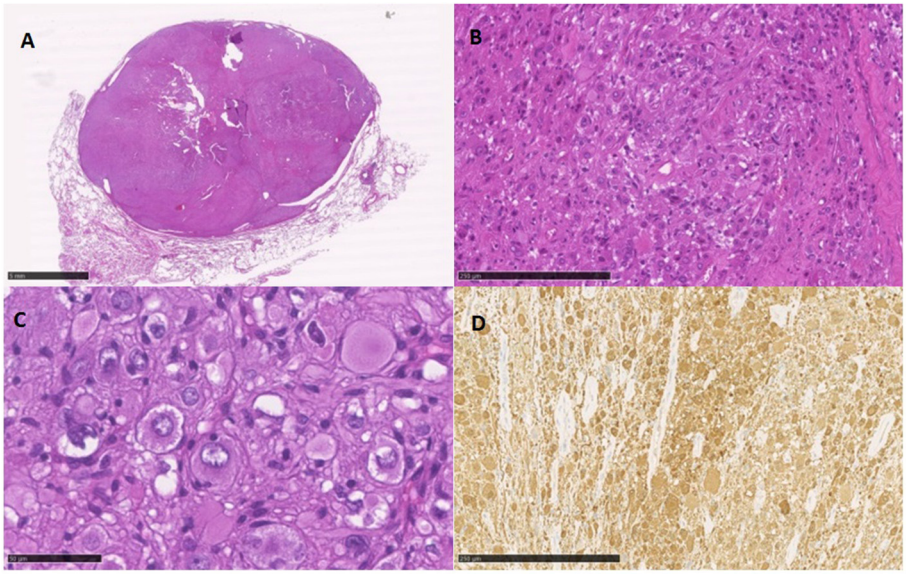


**FIGURE 3 | (A)** low magnification view of the solid, well-defined intrapulmonary neoformation; **(B)** cellular growth is limited by the surrounding fibrous septae; **(C)** the epitheliomorphic ganglion elements are clearly evident with the interposition of some sub-tentacular cells and lymphocytes; **(D)** largely positive immunocytochemical staining for neuron-specific enolase.

Paragangliomas are best evaluated at a contrast-enhanced CT scan, where they show enhancement in the arterial phase (7). However, poor enhancement at a CT scan does not necessarily exclude the diagnosis, but it may be suggestive of a more benign lesion, as it has been reported that the degree of vascularization in non-functioning paragangliomas is not always as rich (5). Silent paragangliomas tend to show mild FDG uptake at a PET scan (5, 7, 8).

These tumors are slow growing and usually benign; however, because they do have a tendency for expansive growth and there are cases reported of low-grade malignant lesions (5, 9), surgical excision, when possible, is the preferred treatment.

In regard to the primary pulmonary paraganglioma, patients have mostly been treated surgically, with either local excision or a lobectomy, depending on the extension of the lesion. No recurrence or metastatic disease has been reported in any of the known cases even though no chemo or radiotherapy was performed afterwards (5, 7). It appears that only 10% of pheochromocytomas and paragangliomas are malignant (4), but there are no biochemical or histological examinations that can reliably predict the tendency of these tumors, and, therefore, surgery remains the only approach to treatment combined with radiologic follow-up.

## CONCLUSIONS

This report presents a case of a primary pulmonary paraganglioma, a rare tumor with only a few cases reported in the literature (5, 7, 8). As the patients are mostly asymptomatic, these tumors are generally discovered incidentally. Surgical excision seems to be the best approach to treatment, followed by radiologic follow-up and no further pharmacological therapy.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

All authors participated equally in the case and in the writing of the manuscript.

## REFERENCES

1. Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and paraganglioma. *N Engl J Med*. (2019) 381:552–65. doi: 10.1056/NEJMra1806651

2. Stenström G, Svärdsudd K. Pheochromocytoma in Sweden 1958–1981. An analysis of the National Cancer Registry Data. *Acta Med Scand*. (1986) 220:225–32. doi: 10.1111/j.0954-6820.1986.tb02755.x

3. Santos P, Pimenta T, Taveira-Gomes A. Hereditary Pheochromocytoma. *Int J Surg Pathol*. (2014) 22:393–400. doi: 10.1177/1066896914537683
4. Brink I, Hoegerle S, Klisch J, Bley TA. Imaging of pheochromocytoma and paraganglioma. *Fam Cancer*. (2005) 4:61–8. doi: 10.1007/s10689-004-2155-y
5. Zhang JJ, Liu T, Peng F. Primary paraganglioma of the lung: a case report and literature review. *J Int Med Res*. (2012) 40:1617–26. doi: 10.1177/147323001204000442
6. Erickson D, Kudva YC, Ebersold MJ, Thompson GB, Grant CS, van Heerden JA, et al. Benign paragangliomas: clinical presentation and treatment outcomes in 236 patients. *J Clin Endocrinol Metab*. (2001) 86:5210–6. doi: 10.1210/jcem.86.11.8034
7. Fiorentino G, Annunziata A, De Rosa N. Primary paraganglioma of the lung: a case report. *J Med Case Rep*. (2015) 9:166. doi: 10.1186/s13256-015-0639-z
8. Huang X, Liang QL, Jiang L, Liu QL, Ou WT, Li DH, et al. Primary pulmonary paraganglioma: a case report and review of literature. *Medicine*. (2015) 94:e1271. doi: 10.1097/MD.0000000000001271
9. Kiziltan HS, Ozucer B, Eris AH, Veyseller B. Bilateral carotid paraganglioma: surgery and radiotherapy. *Clin Med Insights Case Rep*. (2014) 7:53–7. doi: 10.4137/CCRep.S14223

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Surgery

CASE REPORT
published: 26 November 2021
doi: 10.3389/fsurg.2021.754816

# Case Report: Delayed Lung Transplantation With Intraoperative ECMO Support for Herbicide Intoxication-Related Irreversible Pulmonary Fibrosis: Strategy and Outcome

*Guohui Jiao[1†], Xiangnan Li[2†], Bo Wu[1], Hang Yang[1], Guoqing Zhang[2], Zheng Ding[2], Gaofeng Zhao[2*] and Jingyu Chen[1*]*

[1] Wuxi Lung Transplant Center, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi, China, [2] Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

**Background:** Lung transplantation is recognized as the only therapeutic option for patients who develop irreversible pulmonary fibrosis after herbicide intoxication.

**Methods:** We have collected and presented clinical course and outcome of four patients who received lung transplantation due to paraquat and diquat intoxication from 2018 to 2021. Another patient who received initial lung transplantation due to paraquat intoxication and re-transplantation due to chronic lung allograft dysfunction in 2019, was further reported. Patients were admitted in lung transplantation centers, including the 1st affiliated hospital of Zhengzhou University and Wuxi Lung transplantation center. Previous reported cases from Europe, Canada and China were also summarized as benchmark.

**Results:** During the period from the year of 2018 to 2021, there have been four patients in China, who received lung transplantation due to herbicide intoxication. Median age of the four patients was 37 (IQR 34.5, 39.75) years old. Median time from intoxication to lung transplantation was 27.5 (IQR 27, 30.5) days. Bilateral lung transplantation was performed in three patients, while one single lung transplantation was performed in an urgent listed patient. Extracorporeal Membrane Oxygenation (ECMO) and hemopurification support were used in all patients (100%). Details of the cases with follow-ups were further presented and analyzed.

**Conclusions:** Late timing of bilateral lung transplantation can be performed successfully for pulmonary fibrosis after paraquat or diquat intoxication. The survival of patients with complex perioperative conditions can be achieved with a multidisciplinary team to manage the irreversible effects of intoxication.

**Keywords: herbicide, pulmonary fibrosis, lung transplantation, ECMO, hemopurification**

OPEN ACCESS

***Edited by:***
*Nuria Maria Novoa, University of Salamanca Health Care Complex, Spain*

***Reviewed by:***
*Marta Fuentes, University Hospital of Salamanca, Spain*
*Ivan Bravio, Portuguese Institute of Oncology Francisco Gentil, Portugal*

***Correspondence:**
*Gaofeng Zhao*
*zhao_gaofeng@yeah.net*
*Jingyu Chen*
*chenjy@wuxiph.com*

*[†] These authors have contributed equally to this work and share first authorship*

***Specialty section:***
*This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery*

***Received:*** *07 August 2021*
***Accepted:*** *01 November 2021*
***Published:*** *26 November 2021*

***Citation:***
*Jiao G, Li X, Wu B, Yang H, Zhang G, Ding Z, Zhao G and Chen J (2021) Case Report: Delayed Lung Transplantation With Intraoperative ECMO Support for Herbicide Intoxication-Related Irreversible Pulmonary Fibrosis: Strategy and Outcome. Front. Surg. 8:754816. doi: 10.3389/fsurg.2021.754816*

## INTRODUCTION

The compound 1,1′-dimethyl-4,4′-bipyridinium dichloride, known as paraquat, is a widely used, highly toxic contact herbicide that has been banned in many countries. As no antidotes exist, paraquat causes severe and potentially fatal intoxication (1). Other analogs, such as diquat, demonstrates similar pathological changes to the lungs (2). Paraquat can be taken up by the tissues and cleared by the kidney. High levels of paraquat could still be detected as late as 9 weeks after ingestion (3). The lungs have been recognized as the main target organs that are injured by the active accumulation of paraquat, which results in irreversible pulmonary fibrosis. Respiratory failure has been recognized as the main cause of death in the late phase of paraquat intoxication. The current treatments for patients with paraquat poisoning are mostly empirical and supportive, such as early gastric lavage to prevent absorption, emesis induction to promote excretion, laxative administration, and hemoperfusion for detoxification, together with the administration of antioxidants, immunosuppressive agents and even mesenchymal stem cells (4–8).

Since the lung transplantation technique was established, reports have shown that patients suffering from paraquat intoxication could receive lung transplantation as a salvage therapy after exhausting all existing therapeutic regimens (1, 9). Progressive lung damage has been demonstrated without any doubt. Time for considering lung transplantation referral and evaluation, as well as the perioperative support strategy, were discussed in published cases. Here, we summarized the cases performed in China, as well as in the European and North American centers (1968–2017), serving as a useful reference for clinicians in the future.

## PATIENTS AND METHODS

### Study Design and Data Collection

We retrospectively analyzed the medical records of patients from the 1st affiliated hospital of Zhengzhou University (Case 1–4), Wuxi Lung transplantation center and Beijing Chaoyang Hospital (Case 5), submitted to lung transplantation due to herbicide-induced-lung fibrosis or re-transplantation, between 2018 and 2021. Information collected from all patients included demographic data, surgical details, and follow-up data. Another case was admitted and treated in the 1st hospital of Guangzhou Medical University, while detailed data has been reported by Jiang et al. (10). Early cases reported with detailed data from Edinburgh, Toronto and Geneva were also summarized and benchmarked to demonstrate the transition of therapeutic strategy on transplantation timing and perioperative support. Summary of cases are shown in **Table 1**. Continuous data with normal distributions are presented as median with interquartile ranges.

### Ethics

The Institutional Ethics Committees of all centers involved in this study approved the procedures, including verbal consent procedures and data collection. Written informed consent was obtained from the patients and next of kin. The transplanted organs were obtained from volunteer donations, and the next of kin voluntarily provided written informed consent. No lungs were obtained from executed prisoners. The Institutional Ethics Committees of the Organ Procurement Organization approved the donation procedures. Donor lungs were allocated through the China Organ Transplant Response System. The National Transplant Medical Review Board (Chinese Lung Transplantation Society and Transplantation Data Management & Quality Control Center) approved and registered the donors' and recipients' data.

### Perioperative Assessment and Perioperative Management

Preoperative investigations included lab tests, lung function evaluation, functional assessment of other vital organs, and anesthetic evaluation. Preoperative chest X-ray or computed tomography (CT) examinations did not reveal any pulmonary infections or other pulmonary diseases among the donors with $PaO_2/FiO_2$ (P/F) >300 mmHg.

Patients received gastric lavage, antioxidants, immunosuppressive agents, hemopurification as conservative therapy. However, bilateral lung fibrosis still progressed as shown in chest imaging (**Figures 1.1–4A**). Patients had progressively worsening dyspnea and low P/F ratio. Continuous renal replacement therapy, hemoperfusion or hemodialysis was performed due to acute kidney injury in most cases per admitted centers' protocols. Although patients could be stabilized on liver and renal function, while paraquat was not detected in urine, patients could not be weaned from intubation and pulmonary fibrosis progressed. Lung transplantation was thus performed for these patients.

Postoperatively, all patients were admitted in ICU. The immunosuppressive drugs administered included mycophenolate mofetil, tacrolimus, and prednisone. All patients received prophylactic antimicrobial and antiviral medications to prevent bacterial, fungal, and viral infections. Postoperative blood examinations, chest radiography, and bronchoscopy were performed per routine institutional protocol.

## RESULTS AND CASE PRESENTATION

We have collected and reported the details of four cases who received lung transplantation for the 1st time from 2018 to 2021 (Case1–4). The median age of the patients (Case1–4) was 37 (IQR 34.5, 39.75) years old. Median time from intoxication to lung transplantation was 27.5 (IQR 27, 30.5) days. Three patients (75%) received bilateral lung transplantation and ECMO was used for intraoperative support in all four patients (100%). Various ECMO support modes, including venovenous(V-V) (Case 1, 4), venoarterial(V-A) (Case 2, 3) as well as hybrid mode V-AV (Case 3) were all feasible to support patients. Hemopurification, including hemodialysis and hemoperfusion, were used in all patients (100%). The clinical course of Case 1–4 are presented in **Figure 2**. Baseline lab tests and perioperative characteristics were collected and

**TABLE 1 |** Case summary.

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 (Guangzhou,2019) | Case 7 (Edinburgh,1968) | Case 8 (Edinburgh,1973) | Case 9 (Toronto, 1985) | Case 10 (Geneva, 1997) |
|---|---|---|---|---|---|---|---|---|---|---|
| Year | 2018 | 2020 | 2020 | 2021 | 2014/2019* | 2017 | 1968 | 1973 | 1982 | 1995 |
| Gender | Male | Male | Male | Male | Female | Female | Male | Male | Male | Male |
| Age | 45 | 38 | 36 | 30 | 24/29 | 26 | 15 | 18 | 31 | 17 |
| Poison volume/concentration | 60 ml/20% | 50 ml/20% | 80 ml Diquat | 60 ml/20% | 50 ml/20% | 20 ml/20% | 1 mouthful | 1 mouthful | Clothes drenched Chronic exposure | Chronic exposure |
| Poison concentration (ug/ml) at 1st admission | Urine, 229.2 | Urine, 148.6 | Urine,139.7 | Urine, 126.4 | Urine, 248.96 | NR | Blood, 0.4 | | Blood, 0.26 | Lung, 0.134 |
| Gastric Lavage | Yes | Yes | Yes | Yes | Yes | Yes | NR | NR | Yes | NR |
| Hemoperfusion/ dialysis | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| P/F | 150 | 97 | 50 | 124 | 50 | 85 | 70 | 66 | 69 | 69 |
| From poisoning to ECMO bridging (days) | – | – | 26 | – | 44 | – | – | – | – | – |
| From poisoning to LT (days) | 38 | 27 | 27 | 28 | 56 | 58 | 6 | 10 | 32, 51 | 44 |
| Type of LT | Bilateral | Bilateral | Single | Bilateral | Bilateral | Bilateral | Single | Single | Single sequential Right then Left | Single |
| ECMO mode | V-V | V-A | V-A*+ V-AV | V-V | V-V | V-V*+V-A | No | No | V-V | No |
| Post-LT hemodialysis | Yes | Yes | No | No | No | | No | NR | Yes | Yes |
| **Post-LT complication** | | | | | | | | | | |
| Infection | Yes | Yes | Yes | Yes | Yes | Yes | NR | NR | Yes | NR |
| Thrombogenesis | Yes | No | No | No | No | NR | NR | NR | No | NR |
| Bronchial stenosis /Fistula | Yes | No | No | Yes | No | NR | NR | NR | trachea-innominate artery fistula | Bronchopleural fistula |
| Acute pancreatitis | Yes | No | No | No | No | NR | NR | NR | No | No |
| Cardiac failure | No | No | Yes | No | No | NR | NR | NR | No | No |
| Neuromyopathy | No | No | No | No | No | NR | NR | NR | Yes | Yes |
| Survival status | >3 years | >7 months | Death on sepsis | >7 months | Retransplantation on 5th year, survived > 20 months | >1 year | Death on respiratory failure | Death on respiratory failure | Death of massive cerebral infarction | >1 year |

*NR, not reported; *ECMO was used pre-operatively as bridging to lung transplantation.*

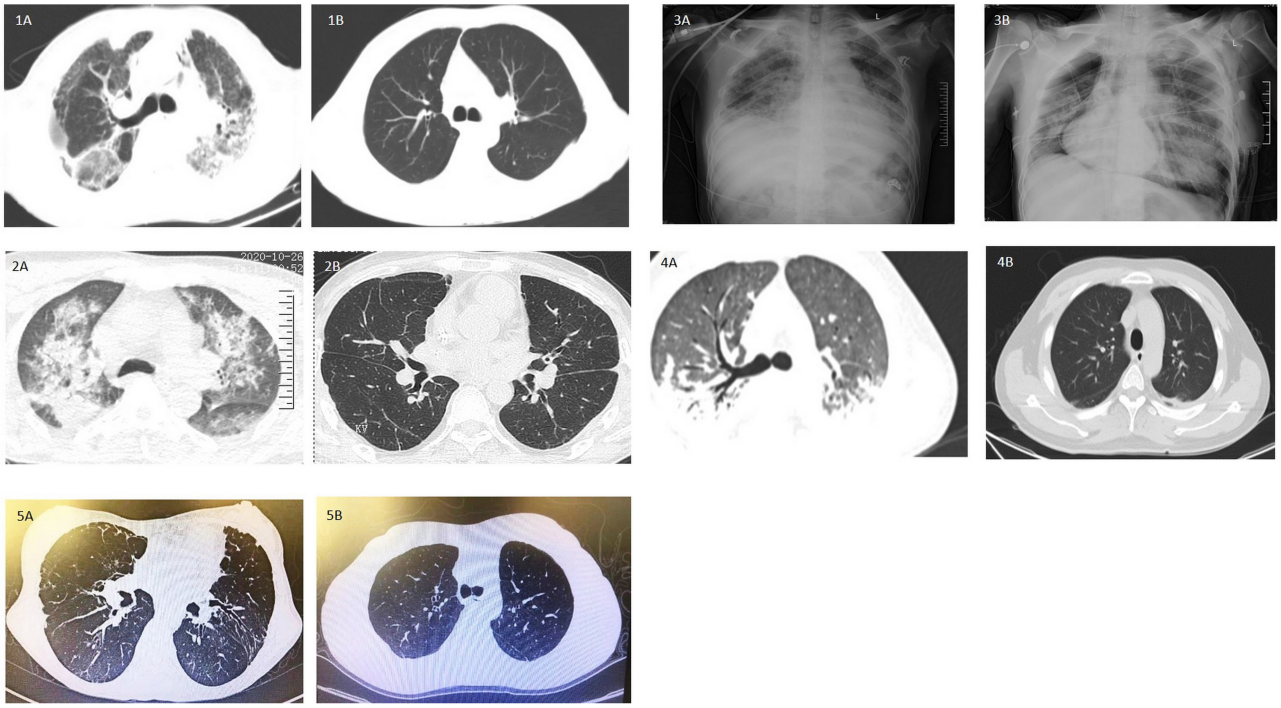


**FIGURE 1 |** CT images of five patients pre-lung transplantation and post-lung transplantation. **(1A–4A)** Progression of bilateral lung fibrosis with consolidation were shown in case 1–4. **(1B, 2B, 4B, 5B)** Post-lung transplantation CT manifestation without significant abnormality. **(3B)** Chest imaging showed significant lung effusion and edema in Case 3. **(5A)** Case 5 suffered deteriorated graft function after 5 years of transplantation and chronic lung allograft dysfunction was suspected.

presented in **Supplementary Table 1**. In addition, we presented the long-term follow-up of another case (Case 5) who received initial lung transplantation due to paraquat intoxication and re-transplantation due to chronic lung allograft dysfunction.

Multiple perioperative complications occurred in these patients. Case 1 developed deep vein thrombosis on postoperative day 2 (POD2) and an inferior vena cava filter was implanted. Acute pancreatitis was diagnosed on POD14 after initiating oral feeding. After receiving conservative therapy as per institutional protocol, patient's status was stabilized and recovered on POD39 and discharged. During the routine follow-up, on POD61, bilateral bronchial stenosis in the proximal termino-terminal bronchial anastomosis was observed. Cryosurgery under bronchoscopy was performed on POD 64, POD67 and POD101 under general anesthesia. Case 4 also experienced bronchial stenosis and was treated by cryosurgery under bronchoscopy. These patients survived to date with improved respiratory symptoms and no obvious lung abnormalities on CT images (**Figures 1.1B**, **4B**). In Case 2, episodes of infection occurred and fully resolved 1 month after lung transplantation. Hemodialysis was continued up to 4 months after surgery. Upon follow-up, patient has fully recovered renal function and pulmonary imaging was normal (**Figure 1.2B**). All these three cases have been regularly followed up in lung transplantation clinics. They survived and returned to work.

Emergent V-A ECMO support for acute respiratory distress syndrome as bridging to lung transplantation was performed in Case 3. Urgent single lung transplantation was performed under V-AV ECMO to improve oxygenation. Mode of ECMO support was transited to V-V ECMO support post-lung transplantation. Cardiac arrhythmia and grade 3 primary graft dysfunction occurred sequentially and could not be wean-off ECMO (**Figure 1.3B**). Patient died on POD12 due to sepsis caused by multi-drug resistant organisms' infection.

From the perspective of long-term outcome, Case 5 had bilateral lung transplantation in the year of 2014 and survived up to 5 years post-lung transplantation. The clinical course of her 1$^{st}$ lung transplantation has been reported previously in detail (11). Patient had progressively worsening dyspnea and headache from the 4$^{th}$ year after surgery. Significant elevation of pulmonary artery pressure (40 mmHg) was detected. Pseudomonas aeruginosa was cultured from sputum. Lung function showed FEV1 0.48 L and FVC 1.19L with deteriorating chest imaging of chronic lung allograft dysfunction (**Figure 1.5A**). Bilateral lung transplantation was performed and postoperative recovery period was uneventful (**Figure 1.5B**). Follow-up lung function showed FEV1 1.9 L, FVC 2.29 L.

## DISCUSSION

Paraquat was introduced to the market as an herbicide in 1962 (12). Diquat is recognized as the second widely used herbicide in the world (13). Over the last few decades, numerous paraquat intoxication cases have been reported,

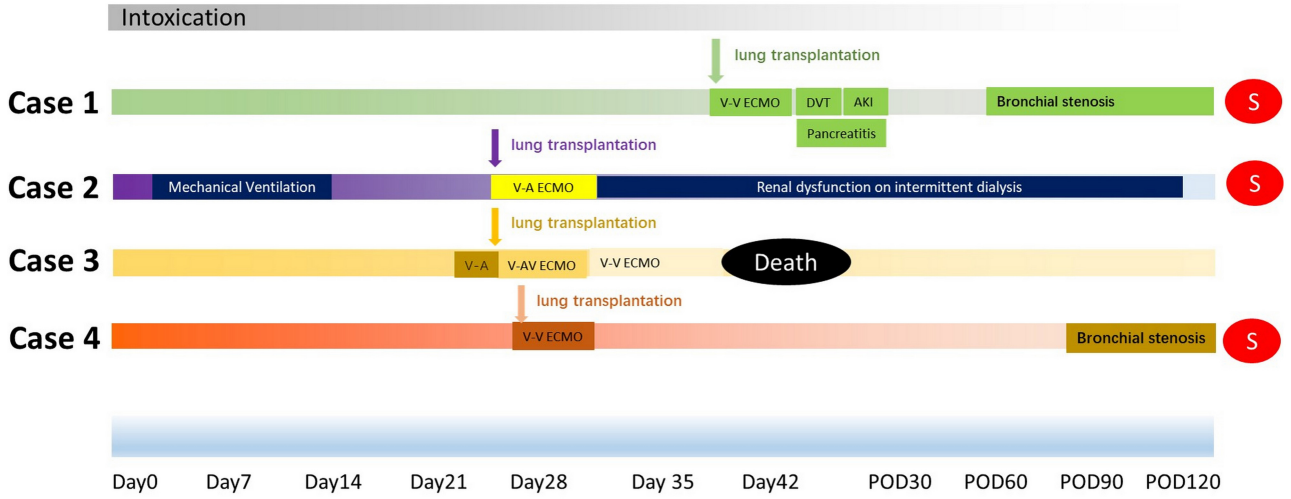


**FIGURE 2 |** Illustration of clinical course and perioperative events in Case 1–4. Pre-lung transplantation and intraoperative mechanical ventilation support, ECMO support modes and duration were illustrated. Post-lung transplantation events were labeled with outcome up to the follow-up date. S, survival; DVT, deep vein thrombosis; AKI, acute kidney injury; POD, post-operation day.

mainly caused by accidental or voluntary ingestion or extensive skin contamination. Much fewer cases of diquat intoxication have been reported in the literature than those of paraquat poisoning, thus, clinicians are still warranted to give attention to its high mortality rate. Due to the abundant polyamine transport systems of type I and II alveolar cells and Clara cells, the lungs are believed to be the main target organ of paraquat poisoning. Paraquat that has accumulated in the lungs and muscle remains even after it is no longer present in blood or urine (14). Mechanism of diquat toxicity is also related to oxidative stress and cell death, aggravating the damage of lungs and kidneys (15).

Respiratory symptoms after intoxication vary from no manifestations to severe shortness of breath, leading to death within as short as 24 h but typically within 2–4 weeks. Treatment strategy for herbicide intoxication, includes gastric lavage, antioxidant therapy, hemoperfusion and hemodialysis as well as immunosuppressive agents. All our patients received the treatments listed above, bilateral pulmonary fibrosis still progressed to the irreversible stage and acute respiratory distress syndrome manifested. All the cases performed in China after 2017 had access to more life support strategies, such as hemopurification and ECMO, which could be used to support organ function and bridge to transplant.

Early cases reported in Europe and Toronto had high mortality rate before 1997 (3, 9, 16, 17). Apart from lack of life-support modalities, single lung transplantation was performed in most cases. All those patients received transplantation within 1 month after intoxication, paraquat could be detected in the blood and death was unavoidable in short term. Toronto team tried secondary contralateral lung transplantation after the initial graft failed. Having been the pioneer of lung transplantation in the world, Toronto team has performed prolonged ECMO support and trachea-innominate artery fistula was well-detected and managed. Death still occurred due to massive cerebral infarction, which is also recognized as the most fatal complication of ECMO.

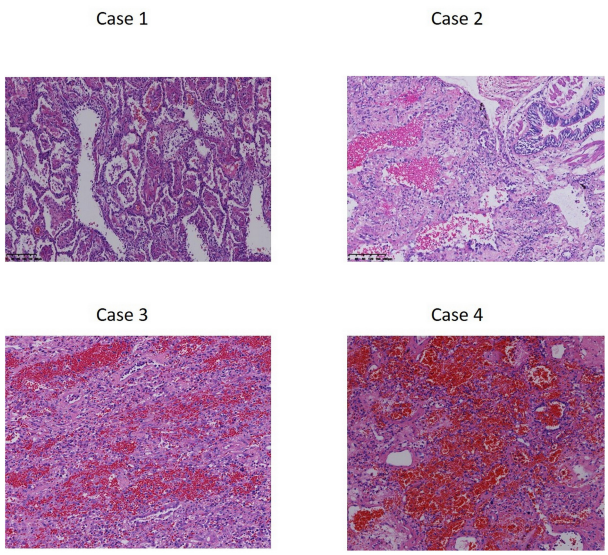


**FIGURE 3 |** Pathology examination of explanted lung tissue after herbicide intoxication. Massive fibroblastic tissue obliterated the lung architecture, with extensive effusions, capillary congestion, inflammatory cell infiltration, alveolar edema, and hyaline membrane formation, could be observed with varied extent of severity in Case 1–4.

The case reported by Geneva team after 1997 achieved long-term survival success (3, 17). Single lung transplantation was performed, however, the time for transplantation was delayed to 44$^{th}$ day, beyond 1 month after intoxication. Toxic neuromyopathy still existed while hemodialysis continued post-lung transplantation. The patient recovered and survived for over 1 year as reported. This case was the first to

demonstrate that late timing of lung transplantation could benefit patients on long-term survival. In our report, patients received lung transplantation after 1 month from intoxication. Further, bilateral lung transplantation was performed in most cases. Only Case 3 received single lung transplantation in an urgent manner and did not survive. Thus, late timing of bilateral lung transplantation might be critical for saving these patients' lives.

Like in other end-stage pulmonary fibrosis patients, ECMO is crucial for intraoperative lung transplantation support and bridging to urgent lung transplantation. While combining with the treatment of hemopurification, more herbicide could be cleared, thus ensuring the long-term benefit for post-lung transplantation survival. In addition, immunosuppressive drugs are also effective for transplantation as well as the intoxication. Poison was not detected in the explanted lungs of our cases. Pathology examination showed extensive effusions, inflammation and congestion in all the intoxicated lungs (**Figure 3**).

Long-term follow-up for these patients is mandated to ensure life quality as they received transplantation in their middle ages. Some of the patients may have unstable emotion before intoxication or even experienced suicidal tendencies. After we evaluated their psychological status thoroughly, we determined to list them as lung transplantation candidates. Close cooperation between doctors and patients is of key importance for maintenance of long-term graft function. The Case 5 patient is a famous singer in China. After re-transplantation, doctors encouraged the patient to continue vocal training and the patient went back to performing on stage. All the patients who were transplanted and survived cherished their lives, continued treatment and followed up regularly in outpatient clinics.

Our experience of successfully treating these patients highlights the efficacy of multi-disciplinary approaches in such complicated scenarios, which could guide clinical practice and inspire the management of these patients who wish to live. Patients after herbicide intoxication showed rapid progression of irreversible pulmonary fibrosis and even acute respiratory distress syndrome. When considering lung transplantation referral timing and strategy, bilateral lung transplantation after 1 month of intoxication with hemopurification and ECMO support will be crucial for long-term survival. These patients warrant physical and psychological rehabilitation during follow-up. Potential intrinsic correlations between poisonous effects and post-operative complications must be explored to further improve quality of life.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Wuxi People's Hospital affiliated to Nanjing Medical University and the First Affiliated Hospital of Zhengzhou University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

JC and GJ: conceptualization. XL and GZhao: resources. BW, HY, GZhang, and ZD: data curation. GJ and XL: writing—original draft preparation. JC and GZhao: writing—review and editing. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.754816/full#supplementary-material

## REFERENCES


1. Cooke NJ, Flenley DC, Matthew H. Paraquat poisoning. Serial studies of lung function. *Q J Med.* (1973) 42:683–92.
2. Wang D, Zhang G, Zhang W, Luo J, Zhu L, Hu J. Successful extracorporeal membrane oxygenation support for severe acute diquat and glyphosate poisoning: a case report. *Medicine.* (2019) 98:e14414. doi: 10.1097/MD.0000000000014414
3. Licker M, Schweizer A, Hohn L, Morel DR, Spiliopoulos A. Single lung transplantation for adult respiratory distress syndrome after paraquat poisoning. *Thorax.* (1998) 53:620–1. doi: 10.1136/thx.53.7.620
4. Meredith TJ, Vale JA. Treatment of paraquat poisoning in man: methods to prevent absorption. *Human Toxicol.* (1987) 6:49–55. doi: 10.1177/096032718700600108
5. Lavergne V, Nolin TD, Hoffman RS, Roberts D, Gosselin S, Goldfarb DS, et al. The EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup: guideline methodology. *Clin Toxicol.* (2012) 50:403–13. doi: 10.3109/15563650.2012.683436
6. Lin JL, Lin-Tan DT, Chen KH, Huang WH, Hsu CW, Hsu HH, et al. Improved survival in severe paraquat poisoning with repeated pulse therapy of cyclo-phosphamide and steroids. *Int Care Med.* (2011) 37:1006–13. doi: 10.1007/s00134-010-2127-7
7. Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. *Brit J Clin Pharmacol.* (2011) 72:745–57. doi: 10.1111/j.1365-2125.2011.04026.x
8. Tsai HL, Chang JW, Yang HW, Chen CW, Yang CC, Yang AH, et al. Amelioration of paraquat-induced pulmonary injury by mesenchymal stem cells. *Cell Transpl.* (2013) 22:1667–1681. doi: 10.3727/096368912X657765
9. Matthew H, Logan A, Woodruff MF, Heard B. Paraquat poisoning–lung transplantation. *Brit Med J.* (1968) 3:759–63. doi: 10.1136/bmj.3.5621.759
10. Jiang WZ, Chen YQ, Zhang YL, Zhang TT, Liu YM, Xu X. Lung transplantation in patients with paraquat poisoning: a case report and literature review. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi.* (2019) 37:292–6. doi: 10.3760/cma.j.issn.1001-9391.2019.04.013
11. Tang X, Sun B, He H, Li H, Hu B, Qiu Z, et al. Successful extracorporeal membrane oxygenation therapy as a bridge to sequential bilateral lung transplantation for a patient after severe paraquat

poisoning. *Clin Toxicol.* (2015) 3:908–13. doi: 10.3109/15563650.2015.1082183
12. Dinis-Oliveira RJ, Duarte JA, Sanchez-Navarro A, Remiao F, Bastos ML, Carvalho F. Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. *Crit Rev Toxicol.* (2008) 38:13–71. doi: 10.1080/10408440701669959
13. Fortenberry GZ, Beckman J, Schwartz A, Prado JB, Graham LS, Higgins S, Lackovic M, et al. Magnitude and characteristics of acute paraquat- and diquat-related illnesses in the US: 1998–2013. *Environ Res.* (2016) 146:191–9. doi: 10.1016/j.envres.2016.01.003
14. Saunders NR, Alpert HM, Cooper JD. Sequential bilateral lung transplantation for paraquat poisoning. A case report. The toronto lung transplant group. *J Thorac Cardiovasc Surg.* (1985) 89:734–42. doi: 10.1016/S0022-5223(19)38729-X
15. Jones GM, Vale JA. Mechanisms of toxicity, clinical features, and management of diquat poisoning: a review. *J Toxicol Clin Toxicol.* (2000) 38:123–8 doi: 10.1081/CLT-100100926
16. Kamholz S, Veith FJ, Mollenkopf F, Montefusco C, Nehlsen-Cannarella S, Kaleya R, et al. Single lung transplantation in paraquat intoxication. *N Y State J Med.* (1984) 84:82–4.
17. Walder B, Bründler MA, Spiliopoulos A, Romand JA. Successful single-lung transplantation after paraquat intoxication. *Transplantation.* (1997) 64:789–91. doi: 10.1097/00007890-199709150-00026

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Surgery

CASE REPORT
published: 01 December 2021
doi: 10.3389/fsurg.2021.772913

# Blunt Trauma Associated With Bilateral Diaphragmatic Rupture: A Case Report

*Marco Pace*[1], *Damiano Vallati*[1], *Elena Belloni*[1], *Marco Cavallini*[1], *Mohsen Ibrahim*[2], *Erino Angelo Rendina*[2] *and Giuseppe Nigri*[1]*

[1] General Surgery Unit, Department of Medical and Surgical Sciences and Translational Medicine, St. Andrea University Hospital, Sapienza University of Rome, Rome, Italy, [2] Thoracic Surgery Unit, Department of Medical and Surgical Sciences and Translational Medicine, St. Andrea University Hospital, Sapienza University of Rome, Rome, Italy

**Background:** A bilateral diaphragmatic rupture is a rare event that occurs in cases of blunt thoracic-abdominal trauma.

**Case Presentation:** We report the case of a 56-year-old female patient with pelvic fracture and second-stage bilateral rupture of the diaphragm due to a car accident. After a chest and abdominal contrast-enhanced computed tomography (CT) scan, the patient underwent emergency suturing of the left hemidiaphragm. On postoperative day (POD) 4, a CT scan performed due to the sudden onset of dyspnea revealed rupture of the right hemidiaphragm, which was not detected on the preoperative CT scan. On POD 9, the right hemidiaphragm was repaired with mesh during a right thoracotomy. The patient recovered 14 days after surgery. However, the postoperative course was complicated by an asymptomatic COVID-19 infection that significantly delayed her discharge from the hospital.

**Conclusions:** Difficulties in preoperative diagnosis and treatment, together with the lack of data in the literature, make this type of trauma a challenge for all acute care and general surgeons.

**Keywords: emergency surgery, blunt trauma, bilateral diaphragmatic rupture, COVID-19, repair of diaphragm, case report**

OPEN ACCESS

***Edited by:***
*Nuria Maria Novoa, University of Salamanca Health Care Complex, Spain*

***Reviewed by:***
*Cecilia Pompili, University of Leeds, United Kingdom*
*Nicolas Moreno-Mata, Ramón y Cajal University Hospital, Spain*

***Correspondence:**
*Giuseppe Nigri*
*giuseppe.nigri@uniroma1.it*

***Specialty section:***
*This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery*

***Received:*** *08 September 2021*
***Accepted:*** *21 October 2021*
***Published:*** *01 December 2021*

***Citation:***
*Pace M, Vallati D, Belloni E, Cavallini M, Ibrahim M, Rendina EA and Nigri G (2021) Blunt Trauma Associated With Bilateral Diaphragmatic Rupture: A Case Report. Front. Surg. 8:772913. doi: 10.3389/fsurg.2021.772913*

## INTRODUCTION

Traumatic diaphragmatic rupture (TDR) is a rare event that follows a thoracic-abdominal blunt trauma, particularly in cases of motor vehicle collisions (1). The incidence of TDR is estimated to be between 0.8 and 8% (1), and it is considered a marker of severe trauma (2). TDR occurs more frequently on the left side of the diaphragm (60–70%), resulting in a concomitant herniation of the stomach, spleen, omentum, and colon (3). In contrast, lesions on the right side are less frequent (15–24%) due to the protective effect of the liver (4). Moreover, there is a point of weakness on the left side, the lumbocostal trigone (5). Bilateral rupture which occurs in only 3% of TDR cases, is a relatively rare event with higher mortality rates (1). We report a case of bilateral TDR in which the rupture of the right diaphragm was initially missed.

## CASE PRESENTATION

A 56-year-old woman who was involved in a car accident was admitted to our emergency room with acute abdominal and pelvic high-pressure compressive trauma. She was alert and oriented, tachycardic, and hypertensive. The patient complained of intense dyspnea and thoracic and abdominal pain. Upon inspection, no ecchymoses or hematomas were detected. On thorax auscultation, a vesicular murmur was absent in the left mid-basal hemithorax. The full-body contrast-enhanced computed tomography (CT) scan showed a left posterolateral diaphragmatic lesion involving the left diaphragmatic pillar and a full stomach herniation resulting in lung parenchyma compression and dislocation of the mediastinum to the right (**Figure 1**). The patient underwent emergent exploratory laparotomy through a bilateral subcostal incision. Abdominal exploration revealed complete herniation of the stomach and spleen into the chest through a 12 cm postero-lateral rupture of the left hemidiaphragm [grade IV, Diaphragm Injury Scale (6)] with the disengagement of the left diaphragmatic pillar. After the stomach and spleen were brought down into the abdomen, the diaphragmatic lesion was sutured with non-absorbable interrupted sutures. No lesions or blood were noted in the suprahepatic region and the Morrison's pouch. A lesion involving the serosa and muscular layers of the transverse colon was repaired using interrupted absorbable sutures. The mucosa was intact and there was no spillage. At the end of the procedure, there were no signs of pneumothorax. Therefore, no pleural drainage was performed.

On postoperative day (POD) 4, the patient complained of sudden onset of mild dyspnea and chest oppression. A new chest and abdomen contrast-enhanced CT scan showed the right liver dome to be raised and the "collar sign" with herniation of the VII and VIII liver segments through a previously undetected right diaphragmatic breach (**Figure 2**). The thoracic surgeons were consulted. As soon the patient was deemed stable by the anesthesiologist, the rupture of the right hemidiaphragm was repaired. On POD 9, a posterolateral thoracotomy at the VI intercostal space was performed. With consideration to the delayed onset of the right hemidiaphragm rupture, thoracotomy was preferred to abdominal access (2, 7) as an abdominal access could result in difficulties due to the presence of the liver. A $10 \times 7$ cm diaphragmatic rupture [grade IV, Diaphragm Injury Scale (6)] was observed with concomitant herniation of the liver segments. The liver was pushed back into the abdomen and the defect was repaired with a DualMesh prosthesis (W. L. Gore & Associates, Inc., Delaware, USA) and interrupted non-absorbable sutures (Video). https://doi.org/10.6084/m9.figshare.16590059. The postoperative course was complicated by non-symptomatic coronavirus disease 2019 infection. This significantly delayed the discharge of the patient.

## DISCUSSION

Bilateral TDR is a very rare event with its incidence reported in only 3% of TDR cases (1). It occurs mainly because of car accidents in which there is a major release of energy. Patients may experience life-threatening injuries to the spleen, kidneys, liver, large and small bowel, lung, thoracic aorta, and abdominal aorta (2.9 vs. 0.2%), as well as multiple fractures of various bones (e.g., pelvic bone, ribs) (1, 4). Although damage to the diaphragm and related complications (herniation and strangulation of the abdominal organs) can be lethal, mortality rates are mainly related to more severe associated injuries (1). Although a delayed diagnosis can increase the mortality and morbidity rates, half of these cases remain undetected, resulting in symptoms such as abdominal pain and respiratory symptoms, years after the acute event (7). Although chest radiography remains the first-level examination, it is diagnostic in only one-third of the cases, compared to chest CT, which is more sensitive (71%) and specific (100%) (4). Chest radiography can recognize diaphragm damage only when the herniated stomach or bowel loops in the chest can be identified (8). Therefore, performing contrast-enhanced CT is mandatory. Through coronal and sagittal CT scans, it is possible to appreciate the pathognomonic signs, namely, the dangling diaphragm sign and the collar sign. The dangling diaphragm sign was first described by Desser et al. as the presence of free edges of the torn diaphragm that take on a comma-shaped appearance and head toward the center of the abdomen (9). The collar sign identifies the imprint of the torn edge of the diaphragm on the herniated organ and is most frequently observed when damage to the left hemidiaphragm causes stomach herniation (8) (**Figure 2**). Once diagnosed, the surgeon must decide when to intervene and which surgical technique to perform. Currently, there are no precise guidelines on the timing of surgery, and it is usually performed when the symptoms and signs become obvious (10). In particular, when there is herniation of the abdominal organs into the thorax due to the pressure difference between the two cavities, early and aggressive surgical treatment reduces the risk of strangulation and perforation of the herniated organs with consequent increase in morbidity and mortality (2).

Another controversial aspect is the surgical approach. The options available to surgeons are laparotomy, thoracotomy, or both if necessary (2). Laparoscopy and thoracoscopy are rarely used because they require a hemodynamically stable patient and a highly skilled surgeon (4, 7). In instances when TDR is diagnosed early, exploratory laparotomy is recommended. In addition to repairing the damage, exploratory laparotomy allows a wide exploration of the abdominal cavity and exclusion of further injuries of the intra-abdominal organs that may not be detected on CT images (7). For patients with a late diagnosis, a thoracotomy is preferable because it allows for better visualization of the relationships between the herniated organs and the pleural cavity for managing adhesions between the abdominal and thoracic organs (2). In our case, our first approach was to perform a laparotomy to check the integrity of the abdominal organs and repair the defect of the left hemidiaphragm, which allowed the lesion on the colonic wall to be repaired. We avoided exploring the right diaphragmatic dome extensively, because there were no clear images of lesion in the preoperative TC, thus avoiding excessive mobilization of the liver. The damage to the right hemidiaphragm, recognized days after the accident, was treated by thoracotomy. According to other studies, we repaired the damage to the left hemidiaphragm

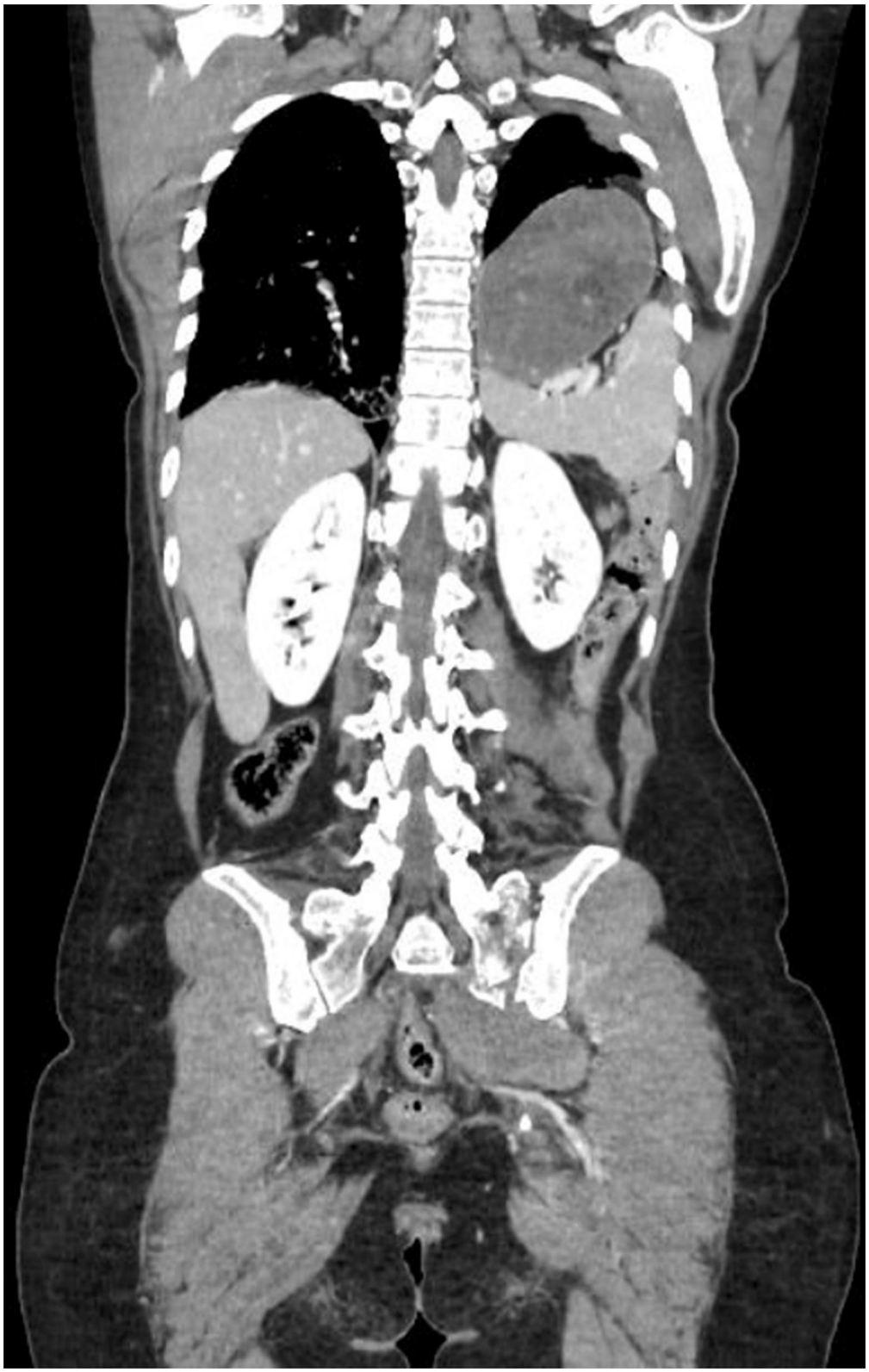

**FIGURE 1 |** Preoperative Thorax-Abdomen contrast-enhanced CT, showing left postero-lateral diaphragmatic lesion involving the left diaphragmatic pillar and the herniation of the stomach and the spleen in thorax, associated with a lung parenchyma compression and dislocation of the mediastinum.

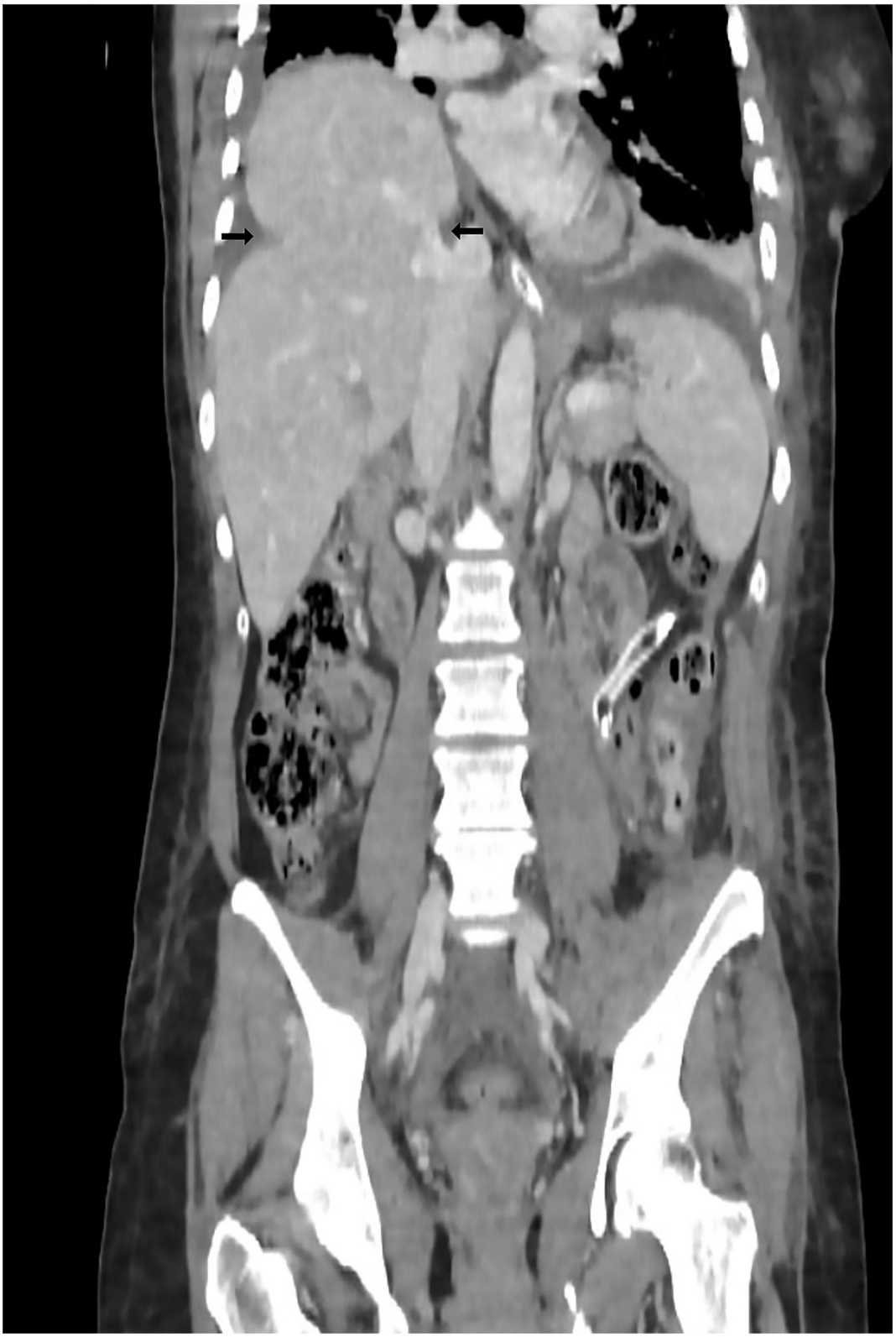

**FIGURE 2 |** Fourth postoperative day Thorax-Abdomen contrast-enhanced CT that showed the raising of the right liver dome and collar sign (black arrows) with herniation of the VII and VIII liver segments.

primarily by taking advantage of the pliability of the diaphragm, which is reduced in cases of delayed diagnosis due to fibrotic processes that prevent the rupture from being repaired primarily (2, 4, 11). The possibility of using a prosthesis was not initially considered because of the colonic lesion. Studies on the use of a biological prosthesis in similar cases have been published. The advantages of using a biological prosthesis include a lower risk of infections, adhesion formation, and erosion into surrounding structures (7, 12).

## CONCLUSION

Bilateral TDR is extremely rare. Given the lack of data, this remains a diagnostic and therapeutic challenge. Although CT provides the most sensitive and specific examination at present, many cases are not diagnosed and remain undetected until they become symptomatic. In terms of treatment options, a gold standard is not available; thus, the choice of treatment is often driven by the experience of the surgeon.

## DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

## ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

MP, DV, and EB gathered the data and drafted the manuscript. MI and GN performed the procedures, drafted, and supervised the manuscript. MC and ER supervised the manuscript. All authors approved the final work.

## REFERENCES


1. Fair KA, Gordon NT, Barbosa RR, Rowell SE, Watters JM, Schreiber MA. Traumatic diaphragmatic injury in the American College of Surgeons National Trauma Data Bank: a new examination of a rare diagnosis. *Am J Surg.* (2015) 209:864–9. doi: 10.1016/j.amjsurg.2014.12.023
2. Gwely NN. Outcome of blunt diaphragmatic rupture. Analysis of 44 cases. *Asian Cardiovasc Thorac Ann.* (2010) 18:240–3. doi: 10.1177/0218492310368740
3. Zarour AM, El-Menyar A, Al-Thani H, Scalea TM, Chiu WC. Presentations and outcomes in patients with traumatic diaphragmatic injury: a 15-year experience. *J Trauma Acute Care Surg.* (2013) 74:1392–8. doi: 10.1097/TA.0b013e31828c318e
4. Al-Jehani Y, Salah A, El-Ghoneimy Y. Bilateral blunt diaphragmatic rupture. *Lung India.* (2011) 28:212. doi: 10.4103/0970-2113.83981
5. Murray JG, Caoili E, Gruden JF, Evans SJ, Halvorsen RA, Mackersie RC. Acute rupture of the diaphragm due to blunt trauma: diagnostic sensitivity and specificity of CT. *Am J Roentgenol.* (1996) 166:1035–9. doi: 10.2214/ajr.166.5.8615237
6. Moore EE, Malangoni MA, Cogbill TH, Shackford SR, Champion HR, Jurkovich GJ, et al. Organ injury scaling iv: thoracic vascular, lung, cardiac, and diaphrag. *J Trauma Acute Care Surg.* (1994) 36:299–300. doi: 10.1097/00005373-199403000-00002
7. Al-Nouri O, Hartman B, Freedman R, Thomas C, Esposito T. Diaphragmatic rupture: is management with biological mesh feasible? *Int J Surg Case Rep.* (2012) 3:349–53. doi: 10.1016/j.ijscr.2012.04.011
8. Bonatti M, Lombardo F, Vezzali N, Zamboni GA, Bonatti G. Blunt diaphragmatic lesions: imaging findings and pitfalls. *World J Radiol.* (2016) 8:819. doi: 10.4329/wjr.v8.i10.819
9. Desser TS, Edwards B, Hunt S, Rosenberg J, Purtill MA, Jeffrey RB. The dangling diaphragm sign: sensitivity and comparison with existing CT signs of blunt traumatic diaphragmatic rupture. *Emerg Radiol.* (2010) 17:37–44. doi: 10.1007/s10140-009-0819-5
10. Ercan M, Aziret M, Karaman K, Bostanci B, Akoglu M. Dual mesh repair for a large diaphragmatic hernia defect: an unusual case report. *Int J Surg Case Rep.* (2016) 28:266–9. doi: 10.1016/j.ijscr.2016.10.015
11. Peker Y, Tatar F, Kahya MC, Cin N, Derici H, Reyhan E. Dislocation of three segments of the liver due to hernia of the right diaphragm: report of a case and review of the literature. *Hernia.* (2007) 11:63–5. doi: 10.1007/s10029-006-0138-7
12. Antoniou SA, Pointner R, Granderath F-A, Köckerling F. The use of biological meshes in diaphragmatic defects - an evidence-based review of the literature. *Front Surg.* (2015) 2:56. doi: 10.3389/fsurg.2015.00056


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Surgery

CASE REPORT
published: 22 April 2022
doi: 10.3389/fsurg.2022.900396

# Case Report: Hemodynamic Instability Caused by Splenic Rupture During Video-Assisted Thoracoscopic Lobectomy

*Chun-tong Liu[1,2], Ting-ting Wu[1,2], Yun-ying Ding[1,2], Jin-long Lin[1,2], Shuang Zhou[1,2], Hong Liu[3], Fu-hai Ji[1,2] and Ke Peng[1,2]*†*

[1]Department of Anesthesiology, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China, [2]Institute of Anesthesiology, Soochow University, Suzhou, Jiangsu, China, [3]Department of Anesthesiology and Pain Medicine, University of California Davis Health System, Sacramento, CA, United States

OPEN ACCESS

**Edited by:**
Nuria Maria Novoa,
University of Salamanca Health Care Complex, Spain

**Reviewed by:**
Yener Aydin,
Faculty of Medicine, Atatürk University, Turkey
Ali Bilal Ulas,
Faculty of Medicine, Atatürk University, Turkey

***Correspondence:**
Ke Peng
pengke0422@163.com

**†ORCID:**
Ke Peng
orcid.org/0000-0003-2879-1759

**Speciality section:**
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

**Received:** 20 March 2022
**Accepted:** 07 April 2022
**Published:** 22 April 2022

**Citation:**
Liu C-t, Wu T-t, Ding Y-y, Lin J-l, Zhou S, Liu H, Ji F-h and Peng K (2022) Case Report: Hemodynamic Instability Caused by Splenic Rupture During Video-Assisted Thoracoscopic Lobectomy. Front. Surg. 9:900396. doi: 10.3389/fsurg.2022.900396

**Background:** Video-assisted thoracoscopic surgery (VATS) has been widely performed for patients with lung cancer. Splenic rupture after VATS lung procedures is a very rare and serious event.

**Case Presentation:** We reported a case with hemodynamic instability after left lower VATS lobectomy. There was no evidence of diaphragmatic injury during the surgery. Computed tomography (CT) showed spleen injury and large amount of fluid in the abdominal cavity. Emergent laparotomy was performed, and splenic rupture was diagnosed. The patient underwent splenectomy, with two lacerations at the diaphragmatic surface of the spleen. The patient did well postoperatively and was discharged from the hospital on postoperative day 5.

**Conclusion:** There are few similar cases reported in the literature. Persistent hemodynamic instability due to the rupture of spleen is life-threatening. In the situation of unexplained hypotension during VATS procedures (especially left-sided approaches), the possibility of splenic injury and rupture should be considered. Abdominal ultrasonography and/or CT examinations should be carried out for prompt diagnosis and treatment of such rare complication.

**Keywords: video-assisted thoracoscopic surgical, splenic rupture, hemodynamic instability, anesthesia management, urgent splenectomy**

## INTRODUCTION

Video-assisted thoracoscopic surgical procedures (VATS) are widely performed for treatment of patients with lung cancer. Growing evidence have shown the advantages of VATS lobectomy over thoracotomy (1). Splenic rupture after VATS lung procedures is a very rare but catastrophic event. Here, we reported a case with persistent hemodynamic instability after VATS lobectomy. After the splenic rupture was eventually diagnosed, the patient received splenectomy. This report adheres to the CARE guidelines, with completed CARE checklist in **Supplementary File S1**.

## CASE REPORT

A 67-year-old female (165 cm height and 68 kg weight) was admitted to our hospital for left lower lung adenocarcinoma and underwent left lower VATS lobectomy. The patient was at American Society of Anesthesiologists physical status II with no major comorbidities. Hemoglobin (Hb) was 11.7 g/dL, and platelet count was $119 \times 10^9$/L. Preoperative laboratory tests revealed no abnormalities in coagulation function or other parameters.

**TABLE 1** | Arterial blood gas and electrolyte analyses.

| Parameter | Timepoint | | | | |
|---|---|---|---|---|---|
| | 21:30 | 22:22 | 00:33 | 01:59 | 02:04 |
| pH | 7.357 | 7.351 | 7.314 | 7.294 | 7.284 |
| $pCO_2$ (mmHg) | 41.1 | 42.3 | 38.8 | 33.7 | 35.4 |
| $pO_2$ (mmHg) | 294 | 66.1 | 73.6 | 96.9 | 93.8 |
| Hb (g/dL) | 8.2 | 8.4 | 8.8 | 6.8 | 7.0 |
| $sO_2$ (%) | 99.9 | 94.2 | 96.2 | 98.4 | 98.1 |
| $O_2Hb$ (%) | 98.4 | 92.0 | 93.7 | 95.7 | 95.7 |
| $K^+$ (mmol/L) | 3.5 | 3.7 | 3.9 | 3.2 | 3.2 |
| $Na^+$ (mmol/L) | 141 | 140 | 139 | 141 | 141 |
| $Ca^{2+}$ (mmol/L) | 1.07 | 1.19 | 1.11 | 1.06 | 1.11 |
| $Cl^-$ (mmol/L) | 112 | 111 | 110 | 112 | 111 |
| Glu (mmol/L) | 7.6 | 10.4 | 15.0 | 12.8 | 13.1 |
| Lac (mmol/L) | 1.5 | 1.6 | 3.8 | 6.3 | 6.9 |
| Hct (%) | 25.2 | 25.7 | 27.1 | 20.9 | 21.4 |
| p50 (mmHg) | 27.57 | 23.98 | 22.37 | 28.68 | 29.14 |
| $HCO_3^-$ std (mmol/L) | 22.5 | 22.6 | 19.4 | 16.8 | 17.0 |
| $HCO_3^-$ (mmol/L) | 23.1 | 23.4 | 19.7 | 16.3 | 16.8 |
| BE(B) (mmol/L) | −2.4 | −2.2 | −6.5 | −10.2 | −9.9 |

Pre-induction non-invasive cuff blood pressure was 142/78 mmHg, heart rate was 72 beats/min, and peripheral oxygen saturation was 97%. The patient received an opioid-free anesthesia regimen. Dexmedetomidine 0.6 μg/kg was administered over 10 min. An arterial line was inserted into the right radial artery for measuring arterial blood pressure. Esketamine 0.3 mg/kg, propofol 2 mg/kg, and rocuronium 0.6 mg/kg were used for induction. A left-sided double-lumen endobronchial tube was used for intubation and confirmed by auscultation, capnography, and fiberoptic bronchoscopy. One-lung ventilation (tidal volume 350–400 mL, respiratory rate 12–18 breaths/min, I/E = 1:2, 60%–100% oxygen) was started. Anesthesia was maintained with sevoflurane 1%–3% inhalation, dexmedetomidine infusion 0.3–1.0 μg/kg/h, and intermittent esketamine boluses 0.1–0.2 mg/kg. Dexamethasone 5 mg and ondansetron 8 mg were given for prophylaxis of postoperative nausea and vomiting.

The surgical procedure started at 16:32. The patient's hemodynamics remained stable for about 3 h into surgery. At 19:30, patient's blood pressure dropped from 130/75 mmHg to 88/51 mmHg. Phenylephrine 50 μg was administered intravenously to treat the hypotension, and dexmedetomidine infusion was also stopped. The anesthesiologist discussed the situation with the thoracic surgeons. They checked the

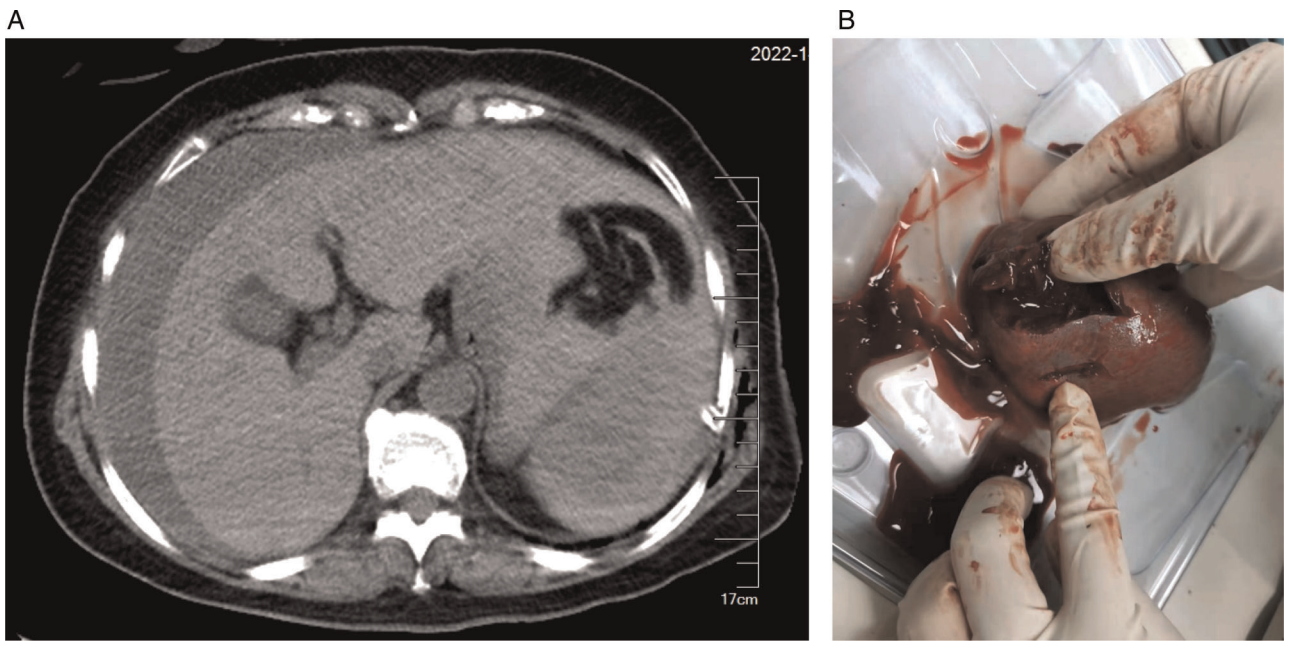


**FIGURE 1** | Images of abdominal computed tomography and ruptured spleen. (**A**) Abdominal computed tomography showing splenic hematoma and large amount of free intraperitoneal fluid. (**B**) Two lacerations of the ruptured spleen.

**TABLE 2** | Hemodynamic changes and treatment for hypotension.

| Parameter | Timepoint | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Baseline (16:00)** | **Start of VATS (16:32)** | **3 h into surgery (19:30)** | **End of VATS (21:00)** | **Tracheal extubation (21:30)** | **1 h post-extubation (22:30)** | **3 h post-extubation (00:30)** | **4.5 h post-extubation (02:00)** | **Start of laparotomy (03:20)** | **End of splenectomy (05:00)** |
| HR (beats/min) | 72 | 69 | 78 | 70 | 87 | 75 | 98 | 101 | 93 | 70 |
| ABP (mmHg) | 142/79 | 143/78 | 88/51 | 105/60 | 89/47 | 81/46 | 102/61 | 120/50 | 83/41 | 104/58 |
| CVP (mmHg) | / | / | / | / | / | / | 6 | 3 | 4 | 8 |
| CI (L/min/$m^2$) | / | / | / | / | / | / | 2.7 | 2.6 | 2.4 | 2.3 |
| SVV (%) | / | / | / | / | / | / | 19 | 7 | 17 | 11 |
| Vasopressors (type and dosage) | / | / | Phenylephrine 50 μg boluses | Boluses of phenylephrine/ ephedrine | Phenylephrine 50–100 μg boluses | Epinephrine 10–20 μg | Norepinephrine, dopamine, or epinephrine | Epinephrine 0.03–0.05 μg/kg/ min | Phenylephrine 50–100 μg boluses | / |
| Other treatment | / | / | Dexmedetomidine stopped | Intravenous fluids | 10% calcium gluconate 10 mL | Methylprednisolone 40 mg | CVC placed, erythrocytes 3 u, FFP 500 mL | Abdominal CT | Erythrocytes 7 u, FFP 500 mL, cryoprecipitate 3 u | Vitamin K1 20 mg, PCC 400 u, fibrinogen 1 g |
| Possible causes for hypotension | / | / | Hypovolemia, surgical bleeding | Hypovolemia | Postoperative bleeding | Myocardial ischemia, cardiogenic shock, and/or anaphylaxis | Hypovolemia and/ or anaphylaxis | Splenic injury, intraperitoneal hemorrhage | Intraperitoneal hemorrhage, hemorrhagic shock | Splenic rupture |

*HR, heart rate; ABP, arterial blood pressure; CVP, central venous pressure; CI, cardiac index; SVV, stroke volume variation; VATS, video-assisted thoracoscopic surgery; CVC, central venous catheter; CT, computed tomography; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma.*

surgical field and found no obvious bleeding. Using intermittent boluses of phenylephrine and/or ephedrine, blood pressure was maintained within 100–130/60–80 mmHg. The surgery was completed at 21:00. Intraoperative fluid infusion consisted of lactate Ringer's solution 1,000 mL and gelatin solution 500 mL. Intraoperative blood loss was approximately 300 mL. Intraoperative urine output was 400 mL.

At the end of the surgery, the arterial blood gas and electrolyte analyses showed that pH = 7.357, $pCO_2$ = 41.1 mmHg, $pO_2$ = 294 mmHg, Hb = 8.2 g/dL, $Ca^{2+}$ = 1.07 mmol/L, and lactate = 1.5 mmol/L (**Table 1**). At 21:30, the double-lumen endobronchial tube was removed after the patient fully awaked. Supplemental oxygen at 2 L/min was delivered via a nasal catheter. Shortly thereafter, her blood pressure dropped from 120/70 mmHg to 85/46 mmHg, and heart rate was 80 beats/min. 10% calcium gluconate 10 mL was administered intravenously. At 22:22, the Hb was 8.4 g/dL (**Table 1**). Blood pressure still fluctuated within 70–100/50–65 mmHg. The surgeons rechecked the drainage and confirmed no bleeding in the chest. At this moment, the patient complained of chest tightness. Myocardial ischemia and cardiogenic shock were suspected. The electrocardiogram showed no abnormality in the ST segment, and high-sensitivity troponin T results did not support myocardial injury. Gelatin anaphylaxis was also considered in the differential diagnosis, and methylprednisolone 40 mg and intermittent low-dose epinephrine 10–20 μg were given intravenously. Bedside chest X-ray ruled out pneumothorax, intrathoracic bleeding, or other intrathoracic abnormalities.

Because of sustained hemodynamic instability, a central venous catheter was placed in the internal jugular vein under ultrasonography, for central venous pressure (CVP) monitoring, fluid resuscitation, and infusion of vasopressors (norepinephrine and dopamine). In addition, cardiac index (CI) and stroke volume variation (SVV) were monitored using the FloTrac/Vigileo system. At 23:55, the monitor showed that CVP = 4 mmHg, CI = 2.6 L/min/$m^2$, and SVV = 19%. Based on these, hypovolemia was considered. Lactate Ringer's solution 500 mL, hydroxyethyl starch 500 mL, erythrocytes 3 units, and fresh frozen plasma 500 mL were given. At 00:33, Hb was 8.8 g/dL, and lactate was 3.8 mmol/L (**Table 1**). Blood pressure was maintained within 100–120/60–80 mmHg, and heart rate was 80–100 beats/min, with a small-dose epinephrine infusion (0.03–0.05 μg/kg/min).

At 01:59, blood analysis showed that pH decreased to 7.294, Hb dropped to 6.8 g/dL, and lactate increased to 6.3 mmol/L (**Table 1**). These results were confirmed by an additional test at 02:04. The patient reported upper abdominal pain, and her abdomen was more distended than before. The bedside abdominal ultrasonography showed free intraperitoneal fluids (images not captured). Abdominal computed tomography (CT) confirmed splenic injury and large amount of fluid in the abdominal cavity (**Figure 1A**). Emergent laparotomy was performed, and splenic rupture was diagnosed. The patient underwent splenectomy, with two lacerations on the diaphragmatic surface of the spleen (**Figure 1B**). The hemodynamic changes and treatment for hypotension of this patient were summarized in **Table 2**. After surgery, the patient was admitted to the thoracic intensive care unit. The patient did well postoperatively. She was transferred to the general ward at postoperative day 1 and discharged from the hospital on postoperative day 5.

## DISCUSSION

Splenic rupture is an uncommon and serious complication of VATS procedures. Only four similar cases were previously reported in the literature (2–5). Among them, one patient was managed with angiographic arterial embolization of the spleen, and the other three patients received splenectomy. Our patient also underwent splenectomy. In all reported cases including our patient, there was no evidence of diaphragmatic laceration during the surgical procedures, and radiographic examinations also showed that the diaphragm was intact. The injury to the spleen may be caused by transdiaphragmatic blunt trauma, which was possibly associated with the positioning of thoracoscopic ports and surgical manipulations. In the absence of diaphragmatic injury during surgery, early diagnosis of splenic rupture is usually difficult. In our case, after excluding hypovolemic shock and surgical bleeding, the cause of hemodynamic instability was considered as cardiogenic shock or anaphylactic shock, and eventually back to hypovolemic shock. We continuously monitored the patient's hemodynamic fluctuations and maintained her blood pressure with vasopressors and volume therapy; however, to some extent, the diagnosis of splenic rupture of this case was delayed.

From this case, we can learn that, in the situation of unexplained hemodynamic instability during the VATS procedures, the possibility of splenic injury and rupture should be considered. For patients with clinical features of hemodynamic instability and abdominal pain after VATS, abdominal ultrasound and/or CT examinations should be carried out as soon as possible for prompt diagnosis and treatment.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the design of this study, data acquisition and interpretation, drafting the manuscript, or revising the manuscript critically. All authors agreed to be accountable for all aspects of the work and gave their final approval of this version to be published. All authors contributed to the article and approved the submitted version.

## FUNDING

Funds from our institution for open access publication fees.

## ACKNOWLEDGMENTS

We would like to thank the thoracic surgeons and our department nurses for their support in this case report.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fsurg.2022.900396/full#supplementary-material.

## REFERENCES

1. Boffa DJ, Dhamija A, Kosinski AS, Kim AW, Detterbeck FC, Mitchell JD, et al. Fewer complications result from a video-assisted approach to anatomic resection of clinical stage I lung cancer. *J Thorac Cardiovasc Surg*. (2014) 148(2):637–43. doi: 10.1016/j.jtcvs.2013.12.045
2. Flores RM, Ihekweazu U, Dycoco J, Rizk NP, Rusch VW, Bains MS, et al. Video-assisted thoracoscopic surgery (VATS) lobectomy: catastrophic intraoperative complications. *J Thorac Cardiovasc Surg*. (2011) 142(6):1412–7. doi: 10.1016/j.jtcvs.2011.09.028
3. Forti Parri SN, Guiducci GM, Domanico A, Tugnoli G. Splenic rupture after videothoracoscopic procedure: an unusual complication conservatively managed. *J Thorac Cardiovasc Surg*. (2014) 148(5):e236–7. doi: 10.1016/j.jtcvs.2014.08.004
4. Zhang Z. A care report of splenic rupture with subcapsular hematoma after thoracoscopic surgery. *Chin J Endosc*. (2001) 5(7):27. [Article in Chinese]. doi: 10.3969/j.issn.1007-1989.2001.05.064
5. Li J, Wang L. Anesthesia management for a patient with splenic rupture during thoracoscopic surgery. *J Clin Anesthesiol*. (2018) 34(3):312. [Article in Chinese]. doi: 10.12089/jca.2018.03.026

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Surgery

CASE REPORT
published: 27 April 2022
doi: 10.3389/fsurg.2022.889753

# Perioperative Management of Patient with Esophageal Carcinoma and Crigler-Najjar Syndrome Type 2: A Case Report

*Dehua Ma*[†], *Fang Chen*[†], *Xiaoyun Chen*[†] *and Yu Chen**

*Department of Chest Surgery, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai, China*

**Background:** Crigler-Najjar syndrome type 2 (CNS-II) is a rare genetic disease that is associated with a lack of uridine diphosphate-glucuronosyltransferase. Esophageal carcinoma is the sixth most common cause of cancer-related death worldwide, for which surgery is the most effective treatment. Reports on patients with both conditions requiring surgery are limited and The impact of hyperbilirubinemia caused by CNS-II on the perioperative period is unknown. Previous studies have found that patients with Crigler-Najjar syndrome have an increased risk of gallstones and related complications, which also poses corresponding challenges to the treatment. Herein, we present a patient with CNS-II who underwent successful thoracoscopic surgery for esophageal carcinoma.

**Case summary:** A 65-year-old male presented to our hospital with a choking sensation after eating. A physical examination showed yellowing of the sclera and skin. The patient manifested persistent jaundice since birth and had visited many hospitals, but the cause remained undiagnosed. We performed genetic testing, which confirmed CNS-II. Gastroscopy indicated esophageal carcinoma. A multidisciplinary team discussion was carried out to determine the appropriate treatment and perioperative management for this patient. The results show that surgical resection was the most appropriate approach. Finally, the patient underwent thoracoscopic surgery for esophageal carcinoma without complications.

**Conclusion:** Esophageal carcinoma in patients with Crigler-Najjar syndrome is a rare case, and perioperative management is key in the treatment process. It is necessary to pay close attention to the changes of the disease to prevent complications.

**Keywords: Esophageal carcinoma, Crigler-Najjar syndrome type 2, case report, esophageal squamous cell carcinoma, surgery, perioperative management**

OPEN ACCESS

***Edited by:***
*Nuria Maria Novoa, University of Salamanca Health Care Complex, Salamanca, Spain*

***Reviewed by:***
*Madara Kreile, Riga Stradiņš University, Latvia*
*Canu Giulia, Azienda USL of Modena, Modena, Italy*

****Correspondence:***
*Yu Chen*
*chenyu5835@126.com*

*[†]These authors have contributed equally to this work*

***Speciality section:***
*This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery*

***Received:*** *04 March 2022*
***Accepted:*** *08 April 2022*
***Published:*** *27 April 2022*

***Citation:***
*Ma D, Chen F, Chen X and Chen Y (2022) Perioperative Management of Patient with Esophageal Carcinoma and Crigler-Najjar Syndrome Type 2: A Case Report. Front. Surg. 9:889753. doi: 10.3389/fsurg.2022.889753*

## INTRODUCTION

Crigler-Najjar syndrome type 2 (CNS-II), also called Arias syndrome, is caused by mutations in *UGT1A1* and is associated with a deficiency in uridine diphosphate-glucoronosyltransferase (UDP-GT) (1, 2). The disorder is transmitted by autosomal recessive inheritance and is characterized by hyperbilirubinemia (3). Existing studies have shown that patients with

Crigler-Najjar syndrome (CN) are at increased risk for gallstones and related complications (4–8), and the early diagnosis of gallstones and cholangitis is challenged due to permanent jaundice. Esophageal carcinoma is an aggressive disease for which surgery is the most effective treatment. However, esophageal carcinoma with simultaneous CNS-II is exceedingly rare, with only a few cases reported thus far. The impact of hyperbilirubinemia on surgical treatment of esophageal cancer is unclear, and its associated complications are unknown. In this paper, we report a patient with CNS-II who underwent successful thoracoscopic surgery for esophageal carcinoma.

# CASE PRESENTATION

## Chief Complaints

A 65-year-old male patient experienced a choking sensation during eating for 2 months.

## History of Present Illness

A 65-year-old male patient was admitted to our hospital because of a choking sensation during eating for 2 months, which was accompanied by retrosternal pain and had no obvious cause.

## History of Past Illness

The patient had a 3-year history of hypertension and took telmisartan for blood pressure control. The patient had manifested yellow discoloration of the skin and sclera since childhood, for which he had visited many hospitals, but his condition did not improve with medication.

## Personal and Family History

The patient's parents were of a consanguineous marriage and had raised three sons and three daughters. Two sons and one daughter also had yellow discoloration while the others showed no relevant symptoms. The patient's daughter and grandson have no relevant symptoms. Its pedigree is shown in **Figure 1**.

## Physical Examination

The patient was generally in a good condition with no supraclavicular lymph node enlargement. The breath sounds of the lungs were rough without rales or Rhonchi. Heart rate was 102 beats/min, and heart rhythm was regular, showing no pathologic murmur. The abdomen was flat and soft, without tenderness or rebound tenderness. Yellow discoloration of the skin and sclera was observed.

## Laboratory Examinations

White blood cell count was $7.0 \times 10^9$/L, neutrophil percentage was 63.1%, hemoglobin concentration was 125 g/L, alanine transaminase was 9 IU/L, aspartate aminotransferase was 18 IU/L, total bilirubin was 187 μmol/L, direct bilirubin was 19.9 μmol/L, and indirect bilirubin was 167.8 μmol/L. Electrocardiography revealed sinus rhythm. we also take a DNA analysis,Genetic testing showed (**Figure 2**):

(1) UGT1A8_ex5 c.1447T > G(p.Tyr483Asp)
(2) UGT1A1_ex1 c.211G > A(p.Gly71Arg)
(3) UGT1A4_ex1 c.395T > C(p.Leu132Pro)

It was suggested that the patient has CNS-II. Other laboratory indicators were all within normal limits.

## Imaging Examinations

Esophagography showed mucosal damage in the mid-to-lower segment of the esophagus, with a filling defect shadow and irregular small niche with a lesion measuring approximately 8.1 cm in length. Gastric endoscopy showed a cauliflower-like ulcero-proliferative growth in the lower part of the esophagus, which was considered to be esophageal squamous cell carcinoma according to the symptoms of the ulcerating surface covered with white moss, and the depressed central part (**Figure 3**).

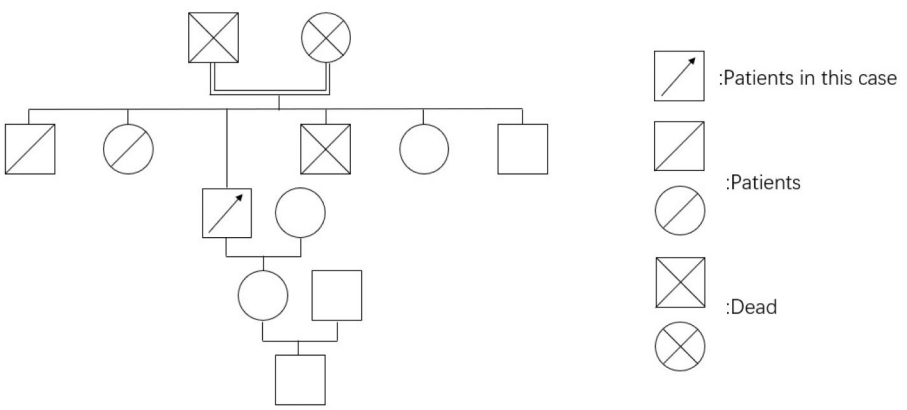


**FIGURE 1** | The pedigree map of the patient's family.

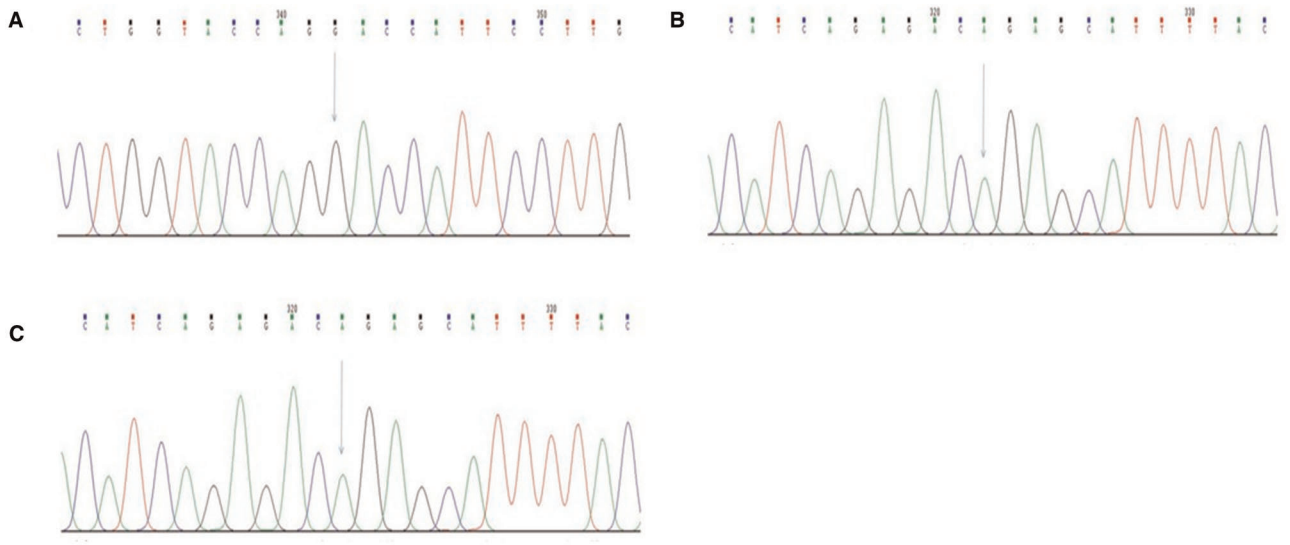


**FIGURE 2** | (**A**) ***UGT1A8***_ex5c.1447T > G(p.Tyr483Asp)NCBI reference sequence: CTGGTACCAG TACCATTCCTTG; (**B**) ***UGT1A1***_ex1c.211G > A(p.Gly71Arg) NCBI reference sequence: CATCAGAGAC GGAGCATTTTAC; (**C**) ***UGT1A4***_ex1c.395T > C(p.Leu132Pro) NCBI reference sequence: GTGGAGCTAC TGCATAATGAGG.

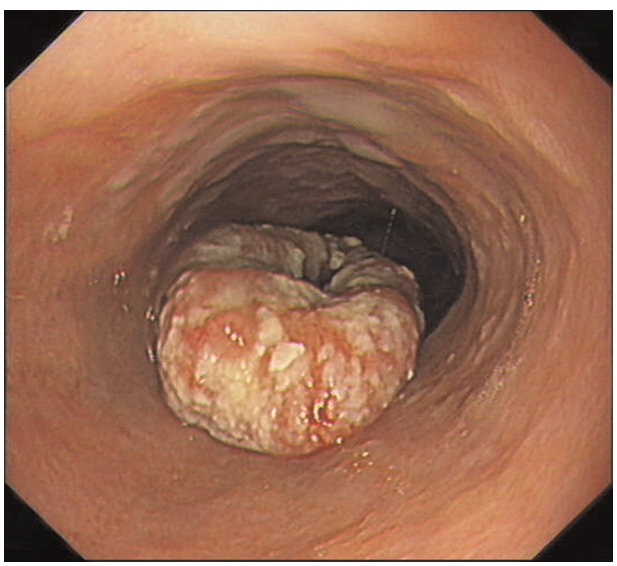

**FIGURE 3** | Gastric endoscopy showed the lower part of the esophagus.

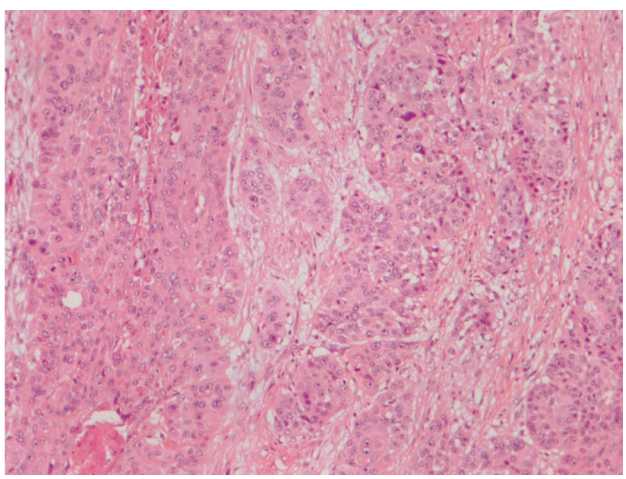

**FIGURE 4** | Microscopic findings show squamous carcinoma, (hematoxylin and eosin staining, magnification × 100).

## FINAL DIAGNOSIS

The final diagnosis was esophageal carcinoma and Crigler-Najjar syndrome type 2.

## TREATMENT

The patient underwent thoracoscopic surgery. Tissue was obtained and sent for pathological examination. The postoperative pathological diagnosis was esophageal squamous cell carcinoma (tumor volume, 7.4 × 5.1 × 1.6 cm). Moderate differentiation was observed with infiltration to the adventitia, and there was no lymph node metastasis (**Figure 4**).

## OUTCOME AND FOLLOW UP

Three months after surgery, the patient revisited our hospital for review. He had recovered well with no related complications, suggesting that the efficacy of surgical treatment was satisfied for this patient with esophageal cancer and CNS-II.

## DISCUSSION

Crigler-Najjar syndrome (CN), which was first described in 1952, is caused by lack of UDP-GT. It can be divided into two categories: type 1 and type 2. Patients with severe jaundice and no response to phenobarbital are classified as Crigler-Najjar syndrome type 1 which type 2 (9).

Crigler-Najjar syndrome type 2 is the less severe form of the disease, with the deficiency in UDP-GT being <30%. UDP-GT is a membrane protein binding on the endoplasmic reticulum, which catalyzes the transfer of the D-Glucuronic acid of UDP – D-Glucuronic acid to other molecules. So it plays play a key part in the Metabolism of bilirubin and promotes the water solubility of acceptors, which promotes the bilirubin excreted from the body by the bile and urine. CNS-II is mostly observed in infants or later in childhood, with bilirubin levels in the region of 102.6–342 mmol/L (10). These patients seldom develop central nervous system involvement complicated by kernicterus. Generally, there are no other notable biochemical parameters, except serum bilirubin. These patients usually survive into adulthood. If the condition becomes serious, it can be treated with phenobarbital to control bilirubin at an appropriate level (11).

Through genetic testing, the patient found three mutated genes, namely UGT1A8, UGT1A1 and UGT1A4. UGT1A8 is a homozygous missense mutation, which has been reported to be detected in Gilbert syndrome and hyperbilirubinemia (12, 13). In vitro functional experiments showed that the mutant protein produced by the mutation had very low scavenging activity against total bilirubin glucuronic acid (13). ClinVar database recorded the mutation as a pathogenic or suspected pathogenic mutation (14). The genetic testing company used SIFT and Polyphen-2 to predict the function of the protein, and the results were both harmful, so the mutation was considered as pathogenic. UGT1A1 is a common variant in Gilbert syndrome and Crigler-Najjar syndrome in the East Asian population (15). In vitro studies have shown that the mutation leads to decreased enzyme activity and is associated with elevated serum bilirubin levels in infants (16). UGT1A1 gene related to CNS-II, Gilbert syndrome (GS), Crigler-Najjar syndrome type 1 (CNS-1) were inherited by autosomal recessive inheritance. As for UGT1A4, ClinVar database has not included this locus, and it is an unknown mutation of clinical significance according to software analysis.

The incidence of CN is approximately at 0.6 patients per million. It is extremely rare for patients with esophageal carcinoma and CNS-II. To the best of our knowledge, this is the first case ever reported. the influence of CN on the occurrence of esophageal cancer is not very well understood, the association CN and early esophageal cancer seen in this case may be incidental. So, there is no experience in this case.

Pre-operative multidisciplinary discussion was held. We all agree that it is important for patients not to suffer starvation for a long period time, which may increase the level of bilirubin. Postoperative vomiting should be avoided by maintaining basal glucose infusion. Ondansetron appears to be efficacious in preventing severe vomiting, but furosemide, salicylates, ampicillin, sulfonamide, and ceftriaxone should be avoided (17). The efficacy of jaundice drugs in the patient was poor, but the jaundice could be reduced. Hepatic encephalopathy may also occur as a postsurgical complication. If necessary, plasma exchange should be performed. Should considerable pruritus occur, phenobarbitals can be used. postoperative parenteral nutrition was administered cautiously to avoid exacerbating jaundice. Should jaundice worsen, bilirubin adsorption is recommended. chemotherapy had a great impact on this patient's liver function, and radiotherapy alone was not adequately effective in treating esophageal cancer, so surgery was the best choice. In terms of surgical options, we chose minimally invasive surgery, which has a similar overall survival rate, lower complications and better tolerance compared with open surgery (18).

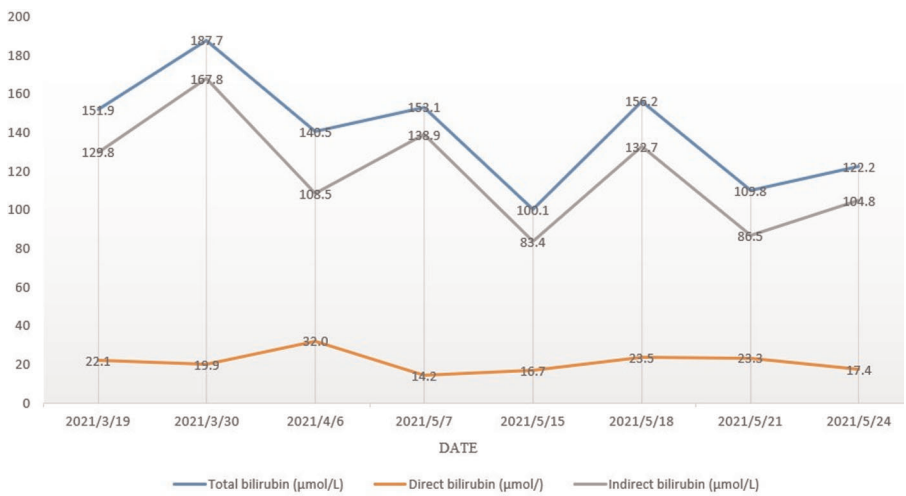


**FIGURE 5** | Changes in the bilirubin during treatment.

Surgery went smoothly, and due to concern for the potential impact on liver function, enteral nutrition rather than parenteral nutrition was adopted. During postoperative hospitalization, certain indicators, including liver function, total bilirubin, direct bilirubin, and indirect bilirubin, were similar to those before surgery (**Figure 5**). The patient was able to drink and eat one week after surgery, and he reported no obvious discomfort. He was discharged two weeks after surgery, without much change in various indicators compared with before surgery. Three months later, the patient revisited our hospital for review and had recovered well, with no related complications. This suggests that the efficacy of surgery was satisfied in this patient with esophageal carcinoma and CNS-II.

CNS-II is a relatively benign disease. The management of the disease involves a variety of methods, including lifelong diet adjustment counseling, ensuring adequate hydration, avoiding triggers such as stress, and lifelong phenobarbital treatment. Genetic counseling, especially about blood relationship, is an important part of management and regular follow-up. For the part of esophageal cancer, the patient has successfully received surgical treatment, and according to the postoperative pathological results, the operation has reached R0 resection, and no lymph node metastasis has been found. It is pT1BN0M0 stage IB, does not need postoperative radiotherapy and chemotherapy, and needs regular follow-up and nutritional support treatment.

## CONCLUSION

Patients with Crigler-Najjar syndrome are at increased risk of various complications due to the presence of persistent hyperbilirubinemia, and the risk of surgical resection may be high, but for diseases that require surgical treatment, surgical treatment can still be performed under close perioperative monitoring and appropriate management.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

## AUTHOR CONTRIBUTIONS

DM, FC, XC wrote the original manuscript and and contributed to literature review; YC contributed to editing the report. All authors contributed to the article and approved the submitted version.

## REFERENCES


1. Liaqat A, Shahid A, Attiq H, Ameer A, Imran M. Crigler-Najjar syndrome Type II diagnosed in a patient with jaundice since birth. *J Coll Physicians Surg Pak*. (2018) 28:806–8.
2. Radlović N. Hereditary hyperbilirubinemias. *Srp Arh Celok Lek*. (2014) 142:257–60. doi: 10.2298/SARH1404257R
3. Strassburg CP. Hyperbilirubinemia syndromes (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor syndrome). *Best Pract Res Clin Gastroenterol*. (2010) 24:555–71. doi: 10.1016/j.bpg.2010.07.007
4. Powell LW, Hemingway E, Billing BH, Sherlock S. Idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome). A study of 42 families. *N Engl J Med*. (1967) 277:1108–12. doi: 10.1056/NEJM196711232772102
5. Foulk WT, Butt HR, Owen CA, Whitcomb FF, Mason HL. Constitutional hepatic dysfunction (Gilbert's disease): its natural history and related syndromes. *Medicine (Baltimore)*. (1959) 38:25–46. doi: 10.1097/00005792-195902000-00002
6. Kagita A, Adachi Y, Kambe A, Kamisako T, Yamamoto T. Type II crigler-Najjar syndrome with intrahepatic cholestasis. *J Gastroenterol*. (1994) 29:214–7. doi: 10.1007/BF02358686
7. Strauss KA, Robinson DL, Vreman HJ, Puffenberger EG, Hart G, Morton DH. Management of hyperbilirubinemia and prevention of kernicterus in 20 patients with Crigler-Najjar disease. *Eur J Pediatr*. (2006) 165:306–19. doi: 10.1007/s00431-005-0055-2
8. Fernandes SR, Moura CM, Rodrigues B, Correia LA, Cortez-Pinto H, Velosa J. Acute cholangitis in an old patient with Crigler-Najjar syndrome type II - a case report. *BMC Gastroenterol*. (2016) 16:33. doi: 10.1186/s12876-016-0449-9
9. Rodrigues C, Vieira E, Santos R, de Carvalho J, Santos-Silva A, Costa E, et al. Impact of UGT1A1 gene variants on total bilirubin levels in Gilbert syndrome patients and in healthy subjects. *Blood Cells Mol Dis*. (2012) 48:166–72. doi: 10.1016/j.bcmd.2012.01.004
10. Canu G, Minucci A, Zuppi C, Capoluongo E. Gilbert and Crigler Najjar syndromes: an update of the UDP-glucuronosyltransferase 1A1 (UGT1A1) gene mutation database. *Blood Cells Mol Dis*. (2013) 50:273–80. doi: 10.1016/j.bcmd.2013.01.003
11. Gailite L, Rots D, Pukite I, Cernevska G, Kreile M. Case report: multiple UGT1A1 gene variants in a patient with Crigler-Najjar syndrome. *BMC Pediatr*. (2018) 18:317. doi: 10.1186/s12887-018-1285-6
12. Maruo Y, Nishizawa K, Sato H, Sawa H, Shimada M. Prolonged unconjugated hyperbilirubinemia associated with breast milk and mutations of the bilirubin uridine diphosphate- glucuronosyltransferase gene. *Pediatrics*. (2000) 106(5):E59. doi: 10.1542/peds.106.5.e59
13. Udomuksorn W, Elliot DJ, Lewis BC, Mackenzie PI, Yoovathaworn K, Miners JO. Influence of mutations associated with Gilbert and Crigler-Najjar type II syndromes on the glucuronidation kinetics of bilirubin and other UDP-glucuronosyltransferase 1A substrates. *Pharmacogenet Genomics*. (2007) 17(12):1017–29. doi: 10.1097/FPC.0b013e328256b1b6
14. Lin R, Wang X, Wang Y, Zhang F, Wang Y, Fu W, et al. Association of polymorphisms in four bilirubin metabolism genes with serum bilirubin in three Asian populations. *Hum Mutat*. (2009) 30(4):609–15. doi: 10.1002/humu.20895
15. Teng HC, Huang MJ, Tang KS, Yang SS, Tseng CS, Huang CS. Combined UGT1A1 and UGT1A7 variant alleles are associated with increased risk of Gilbert's syndrome in Taiwanese adults. *Clin Genet*. (2007) 72(4):321–8. doi: 10.1111/j.1399-0004.2007.00873.x
16. Yamamoto A, Nishio H, Waku S, Yokoyama N, Yonetani M, Uetani Y, et al. Gly71Arg mutation of the bilirubin UDP-glucuronosyltransferase 1A1 gene is associated with neonatal hyperbilirubinemia in the Japanese population. *Kobe J Med Sci*. (2002) 48(3-4):73–7.
17. Bicak M, Akelma H, Salik F, Kaya S. Combined spinal and TAP blocks for laparoscopic cholecystectomy for a patient with Crigler-Najjar Type 2: a case report. *Niger J Clin Pract*. (2020) 23:1772–5. doi: 10.4103/njcp.njcp_19_20

18. Voron T, Lintis A, Piessen G. Hybrid esophagectomy. *J Thorac Dis*. (2019) 11:S723–7. doi: 10.21037/jtd.2018.12.92

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Surgery

ORIGINAL RESEARCH
published: 06 May 2022
doi: 10.3389/fsurg.2022.893429

# Better Prognosis and Survival in Esophageal Cancer Survivors After Comorbid Second Primary Malignancies: A SEER Database-Based Study

*Jiayue Ye†, Sheng Hu†, Wenxiong Zhang, Deyuan Zhang, Yang Zhang, Dongliang Yu, Jinhua Peng, Jianjun Xu* and Yiping Wei**

*Department of Thoracic Surgery, The Second Affiliated Hospital of Nanchang University, Nanchang, China*

OPEN ACCESS

**Edited by:**
*Nuria Maria Novoa, University of Salamanca Health Care Complex, Spain*

**Reviewed by:**
*Elena Prisciandaro, University Hospitals Leuven, Belgium*
*Carmelina Cristina Zirafa, Robotic Multispeciality Center for Surgery, University Hospital of Pisa, Italy*

***Correspondence:**
*Jianjun Xu*
*xujianjun3526@163.com*
*Yiping Wei*
*weiyip2000@hotmail.com*

†*These authors have contributed equally to this work*

**Specialty section:**
*This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery*

**Received:** *10 March 2022*
**Accepted:** *25 April 2022*
**Published:** *06 May 2022*

**Citation:**
*Ye J, Hu S, Zhang W, Zhang D, Zhang Y, Yu D, Peng J, Xu J and Wei Y (2022) Better Prognosis and Survival in Esophageal Cancer Survivors After Comorbid Second Primary Malignancies: A SEER Database-Based Study. Front. Surg. 9:893429. doi: 10.3389/fsurg.2022.893429*

**Background:** With the development of surgical techniques and advances in systemic treatments, the survival time of esophageal cancer survivors has increased; however, the chance of developing a second primary malignancy (SPM) has also increased. These patients' prognosis and treatment plans remain inconclusive.

**Objectives:** We aimed to evaluate and predict the survival of patients with esophageal cancer with second primary tumors, to provide insights and the latest data on whether to pursue more aggressive treatment.

**Materials and Methods:** We selected esophageal cancer cases from the latest available data from the SEER database on April 15, 2021. We performed life table analysis, Kaplan–Meier analysis, and univariate and multivariate Cox proportional hazards analysis to assess the patient data. We conducted multiple Cox regression equation analyses under multiple covariate adjustment models, and performed a stratified analysis of multiple Cox regression equation analysis based on different covariates. To describe our study population more simply and clearly, we defined the group of patients with esophageal cancer combined with a second primary malignant tumor (the first of two or more primaries) as the EC-SPM group.

**Results:** Our analysis of 73,456 patients with esophageal cancer found the median survival time of the EC-SPM group was 47.00 months (95% confidence interval (CI), 43.87–50.13), and the mean survival time was 74.67 months (95% CI, 72.12–77.22). Kaplan–Meier curves of different esophageal cancer survivors showed that the survival of the EC-SPM group was significantly better than that of the other groups ($p < 0.01$).

**Abbreviations:** EC, esophageal cancer; SEER, Surveillance, Epidemiology, and End Results database; SPM, second primary malignancy; HR, hazard ratio; CI, confidence interval; EC-SPM, Esophageal cancer patients with second primary malignant cancer.

Univariate Cox regression analysis showed that compared with only one malignancy only group, the hazard ratio (HR) of the EC-SPM group was 0.95 (95% CI, 0.92–0.99; $p < 0.05$). In the multivariate Cox regression analysis under different adjustment models, the EC-SPM group had a reduced risk of death compared with the one primary malignancy only group (HR < 1, $p < 0.05$).

**Conclusion:** Survivors of esophageal cancer with a second primary malignant cancer have a better prognosis, but require more aggressive treatment. This study provided new evidence and new ideas for future research on the pathophysiological mechanism and treatment concepts of esophageal cancer combined with SPM.

**Keywords: esophageal cancer survivors, second primary malignant cancer, SEER, survival, prognosis**

## INTRODUCTION

Esophageal cancer (EC) is the seventh most common cancer in the world and the sixth leading cause of cancer death (1, 2). In recent years, with the progress of surgical technology and systematic treatment, the survival time of patients with cancer has improved significantly (3). Therefore, the problem of cancer survivors complicated with a second primary malignant tumor (SPM) has become more prominent (4, 5). The treatment plan for patients with esophageal cancer combined with an SPM has not yet been finalized, which poses new challenges for clinicians (6, 7).

SPM refers to tumor occurrence in a single or multiple organs of the same individual, developing after the first primary malignancy, independent of the first primary malignancy, rather than through metastasis or recurrence (8). Mechanistic research into SPM is vague, showing that it might be related to genetics (9), treatment-related exposures (such as radiation therapy) (10), and behavior-related factors (11).

In the past, patients with esophageal cancer with SPM were considered at risk of poor prognosis, and more aggressive treatment might be abandoned as a result. Previous studies had limitations, such as obsolete data and cases that could not represent the esophageal cancer population adequately; therefore, their conclusions were controversial (3, 12–18). Currently, there is no relevant prospective research, and the presence of controversial research makes it difficult for clinicians to guide treatment plans accurately. Surveillance, Epidemiology, and End Results (SEER) is the authoritative source of cancer statistics in the United States. The SEER database released the most recent esophageal cancer follow-up data on April 15, 2021. Therefore, the data sources are very representative. A comprehensive understanding of the prognosis and influencing factors of esophageal cancer with SPM might provide new evidence and support for future research on disease mechanisms and treatment concepts.

Our objective was to further investigate the true survival of patients with esophageal cancer combined with SPM based on the latest data, providing an update on the evidence that such patients should be treated more aggressively.

## MATERIALS AND METHODS

### Data Sources

Data for our study were obtained from the SEER database (https://www.cancer.gov) on April 15, 2021, and we included data from 18 US states from 2000 to 2018 (including San Francisco Oakland standard metropolitan statistical area (SMSA), Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose Monterey, Los Angeles, Alaska Natives, rural Georgia) California, Kentucky, Louisiana, New Jersey, and greater Georgia) comprising records of patients with newly diagnosed esophageal cancer. All patients with esophageal cancer were included in our study. Data for the study's exposure variables and dependent variables were complete, with no missing values. Missing values for some covariates were imputed as an independent group and named "unknown". Our study covered 27.8% of the US population (based on the 2010 Census). We selected 13 entries including ID, survival months (the median and mean survival time of patients with esophageal cancer and a second primary malignancy was calculated from the date of diagnosis of esophageal cancer), status, year of diagnosis, sex, age, ethnicity (White, Black, Asian, Pacific Islander and Native American/Native Alaskan), International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histological type, primary site, grade (through 2017), summary stage 2000 (1998–2017), median household income inflation-adjusted to 2019, regional nodes positive (1988+), and a total number of in situ/malignant tumors for the patient. Institutional review board approval was not necessary because the SEER database is publicly available.

### Data Grouping

Individual entries were integrated and grouped (**Supplementary Tables S1**, **S2**). To conduct the study more clearly and simply, we defined the group having the 1st of two or more primaries in our study as the EC-SPM group. There were no missing values for age, primary site, and histological type (ICD-O-3) and a small number of missing values for other variables;

however, these were all rank or quantile variables given a fill-in using the median or mode.

## Data Processing and Statistical Analysis

We use frequency function statistics, and SPSS v. 24 (IBM Corp., Armonk, NY, USA) for the statistical analysis. We used GraphPad Prism 8 (GraphPad Inc., La Jolla, CA, USA) to plot the trend of median survival time in the different subgroups. Data were analyzed using statistical packages R version 3.6.3 (R Foundation, http://www.r-project.org) and Empower Stats (www.empowerstats.net, X&Y solutions Inc., Boston, Massachusetts). *P* value <0.05 was considered statistically significant. Life table, Kaplan–Meier, and univariate and multivariate Cox proportional hazards analyses were used to study the differences in prognosis and we performed overall analysis and stratified analysis using multivariate Cox regression with multiple adjustment models using sequence number as the exposure variable. Model I was not adjusted. Model II was adjusted for age, sex, and ethnicity. Model III was adjusted according to age, sex, ethnicity, histological type, summary stage, regional nodes positive, primary site, and household income. Log rank (Mantel-Cox), Breslow (generalized Wilcoxon), and Tarone–Ware tests were used to compare the distribution of survival data between the groups.

# RESULTS

There were 73,456 patients diagnosed with esophageal cancer entered into the SEER database from 2000 to 2017, of which 77.31% were male, 69.36% were under 75 years old, 46.24% were in the esophageal squamous-cell carcinoma (ESCC) group, 20.08% were in the localized group, the lymph nodes not examined group account for 77.67%, the lower third of esophagus group accounted for 56.50%, and the income group less than $75,000 accounted for 69.99%. The remaining baseline data for the populations are presented in **Table 1**. The comparison of median survival time and the growth rate of each group is shown in **Supplementary Figure S1**.

## Better Survival and Prognosis in Patients With Esophageal Cancer Combined With SPM

### The Survival Advantage of Patients with Esophageal Cancer Combined With SPM

The median survival time of the 73,456 patients was 10.00 months (95% confidence interval (CI), 9.87–10.14), the mean survival time was 33.44 months (95% CI, 32.95–33.93), and the five-year survival rate was 14% ($p < 0.01$). The median survival time of the EC-SPM group was 47.00 months (95% CI, 43.87–50.13), the mean survival time was 74.67 months (95% CI, 72.12–77.22), and the five-year survival rate was 39% ($p < 0.01$). The median survival time of the one primary malignancy only group was 9.00 months (95% CI, 8.86–9.14), the mean survival time was 32.16 months (95% CI, 31.58–32.74), and the five-year survival rate was 13% ($p < 0.01$). The median survival time of the 2nd of two or more primaries group was 9.00 months (95% CI, 8.69–9.32), the mean survival time was 27.94 months (95% CI, 26.95–28.93), and the five-year survival rate was 12% ($p < 0.01$). The median survival time of the 3rd of three or more primaries group was 8.00 months (95% CI, 7.42–8.58), the mean survival time was 23.18 months (95% CI, 21.44–24.93), and the five-year survival rate was 9% ($p < 0.01$) (**Table 2** and **Supplementary Data Sheet S1**). The overall median survival time growth rate was 15.98%, the median survival time growth rate was 18.43% in the one primary only group, and the median survival time growth rate was decreased in the EC-SPM group (**Figure 1** and **Supplementary Data Sheet S2**).

### Kaplan–Meier Curves for Survival Advantage of Patients With Esophageal Cancer Combined With SPM

Kaplan–Meier curves of the different groups of esophageal cancer survivors showed that the survival of the EC-SPM group was significantly better than that of the other groups ($p < 0.01$; **Figure 2**). The survival rate of the one primary malignancy only group was higher than that of 3rd of three or more primaries group ($p < 0.05$); and the survival rate of the 2nd of three or more primaries group was higher than that of the 3rd of three or more primaries group ($p < 0.05$; **Figure 3** and **Table 3**). The Log-rank (Mantel–Cox) test, Breslow (generalized Wilcoxon) test, and Tarone–Ware test were used to indicate significant chi squared and *p*-values for survival differences in the between group comparisons (**Table 3**).

### Univariate and Multivariate Cox Regression Analysis of Survival Advantage in Patients with Esophageal Cancer with SPM

Univariate Cox regression analysis revealed a 5.00% reduction in the risk of death in the EC-SPM group compared with that in the reference group (95% CI, 0.92–0.99; $p < 0.05$) (**Table 4**). Using sequence number as the exposure variable, survival time as the time variable, status as the outcome variable, and one primary only group as the reference group, Cox multiple regression equation analysis was performed in different models of adjustment (total analysis and stratified analysis) (**Table 5**). The results of the overall analysis showed that under Model I, the risk of death in the EC-SPM group was 53% lower than that in the reference group (95% CI, 0.45–0.49; $p < 0.01$). After adjustment in model II, the risk of death in the EC-SPM group was reduced by 53% (95% CI, 0.45–0.48; $p < 0.01$). After adjustment for Model III, the risk of death in the EC-SPM group was reduced by 49% (95% CI, 0.49–0.53; $p < 0.01$). When adjusted according to model III, the risk of death in the EC-SPM group was reduced in the subgroups of age, sex, ethnicity, histological type, summary stage, primary site, lymph node positive, and household income (hazard ratio (HR) <1, $p < 0.05$). The more detailed results, the 95% CI, and *p*-values are shown in **Table 5**.

**TABLE 1** | Baseline characteristics of participants ($N = 73,456$).

| Sequence number | *N* (%) | One primary only | 1st of 2 or more primaries | 2nd of 2 or more primaries | 3 or more primaries | *p*-value |
|---|---|---|---|---|---|---|
| **Sex (%)** | | | | | | <0.01 |
| Female | 16671 (22.69%) | 21.8 | 21.2 | 24.6 | 32.8 | |
| Male | 56785 (77.31%) | 78.2 | 78.8 | 75.4 | 67.2 | |
| **Age (%)** | | | | | | <0.01 |
| ≤74 years | 50951 (69.36%) | 73.0 | 77.0 | 56.3 | 47.3 | |
| 75+ years | 22505 (30.64%) | 27.0 | 23.0 | 43.7 | 52.7 | |
| **Race (%)** | | | | | | <0.05 |
| White and other races | 65303 (88.90%) | 88.8 | 88.0 | 89.0 | 90.5 | |
| Black | 8153 (11.10%) | 11.2 | 12.0 | 11.0 | 9.5 | |
| **Histologic type (%)** | | | | | | <0.01 |
| Adenocarcinomas | 39491 (53.76%) | 55.3 | 54.5 | 49.9 | 41.3 | |
| Squamous cell neoplasia and other types | 33965 (46.24%) | 44.7 | 45.5 | 50.1 | 58.7 | |
| **Summary stage (%)** | | | | | | <0.01 |
| Localized | 14750 (20.08%) | 17.7 | 34.6 | 24.2 | 26.4 | |
| Regional | 34937 (47.56%) | 47.1 | 48.2 | 48.7 | 51.3 | |
| Distant | 23769 (32.36%) | 35.2 | 17.2 | 27.1 | 22.2 | |
| **Regional nodes positive (%)** | | | | | | <0.01 |
| Lymph nodes not examined | 57053 (77.67%) | 77.3 | 66.4 | 81.1 | 85.5 | |
| Lymph nodes were negative | 8871 (12.08%) | 11.9 | 22.3 | 10.6 | 8.4 | |
| Lymph nodes were positive | 7532 (10.25%) | 10.9 | 11.3 | 8.3 | 6.1 | |
| **Primary site (%)** | | | | | | <0.01 |
| Lower third of esophagus | 41502 (56.50%) | 57.8 | 58.7 | 52.4 | 46.2 | |
| Other sites | 31954 (43.50%) | 42.2 | 41.3 | 47.6 | 53.8 | |
| **Income (%)** | | | | | | <0.01 |
| <$75,000 | 51412 (69.99%) | 70.5 | 69.5 | 68.6 | 67.2 | |
| $75,000+ | 22044 (30.01%) | 29.5 | 30.5 | 31.4 | 32.8 | |
| **Sequence number** | | | | | | <0.01 |
| One primary only | 54219 (73.81%) | 100 | 0 | 0 | 0 | |
| 1st of 2 or more primaries | 3923 (5.34%) | 0 | 100 | 0 | 0 | |
| 2nd of 2 or more primaries | 12394 (16.87%) | 0 | 0 | 100 | 0 | |
| 3 or more primaries | 2920 (3.98%) | 0 | 0 | 0 | 100 | |
| **Status (%)** | | | | | | <0.01 |
| Alive | 12222 (16.64%) | 16.3 | 28.4 | 15.0 | 14.2 | |
| Dead | 61234 (83.36%) | 83.7 | 71.6 | 85.0 | 85.8 | |

*Note: (a) Other ethnicities included Asian, Pacific Islander and Native American/Native Alaskan.*
*(b) Other types included the histological types of esophageal cancer except for adenocarcinoma and squamous cell carcinoma.*
*(c) Others included C15.0-Cervical esophagus, C15.1-Thoracic esophagus, C15.2-Abdominal esophagus, C15.3-Upper third of esophagus, C15.4-Middle third of esophagus, C15.8-Overlapping lesion of esophagus, and C15.9-Esophagus, NOS.*

## Variables Influencing the Survival of Patients with Esophageal Cancer

The median survival time and mean survival time of the different groups with different covariates are described in detail in **Supplementary Data Sheet S1**. The younger than 75 years old group, the non-black group, the adenocarcinomas group, the limited group, the lymph node negative group, and the lower third of the esophageal group had a longer median survival time (**Supplementary Figure S2, Data Sheet S1**). Kaplan–Meier survival curves of the different covariates showed significant differences in overall survival rates between the different groups, $p < 0.01$ (**Supplementary Figure S2** and **Table 2**).

Univariate Cox regression analysis shows that compared with the reference group, the group younger than 75 years old

**TABLE 2** | The 3-year and 5-year survival rates of patients with esophageal cancer; Median and mean survival time of patients with esophageal cancer.

| | Percentage of total patients (%) | 3-year survival rate (%) | Probability density | 5-year survival rate (%) | Probability density | 10-year survival rate (%) | Probability density | Median survival time (months) | Standard Error | 95.0%, CI | | Mean survival time (months) | Standard Error | 95.0%, CI | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Lower | Upper | | | Lower | Upper |
| **Total** | 100.00 | 18.00 | <0.01 | 14.00 | <0.01 | 9.00 | <0.01 | 10.00 | 0.07 | 9.87 | 10.14 | 33.44 | 0.25 | 32.95 | 33.93 |
| **Sex** | | | | | | | | | | | | | | | |
| Female | 22.70 | 18.00 | <0.01 | 14.00 | <0.01 | 9.00 | <0.01 | 9.00 | 0.14 | 8.72 | 9.28 | 33.26 | 0.52 | 32.25 | 34.27 |
| Male | 77.30 | 18.00 | <0.01 | 14.00 | <0.01 | 9.00 | <0.01 | 10.00 | 0.08 | 9.85 | 10.15 | 33.48 | 0.28 | 32.93 | 34.04 |
| **Age** | | | | | | | | | | | | | | | |
| <75 years | 69.40 | 24.00 | <0.01 | 18.00 | <0.01 | 12.00 | <0.01 | 11.00 | 0.10 | 10.81 | 11.19 | 39.84 | 0.33 | 39.18 | 40.49 |
| 75+ years | 30.60 | 13.00 | <0.01 | 8.00 | <0.01 | 3.00 | <0.01 | 6.00 | 0.09 | 5.83 | 6.17 | 18.95 | 0.26 | 18.44 | 19.46 |
| **Race** | | | | | | | | | | | | | | | |
| White and other races (a) | 88.90 | 21.00 | <0.01 | 16.00 | <0.01 | 10.00 | <0.01 | 10.00 | 0.07 | 9.86 | 10.14 | 34.70 | 0.27 | 34.17 | 35.23 |
| Black | 11.10 | 14.00 | <0.01 | 10.00 | <0.01 | 5.00 | <0.01 | 7.00 | 0.15 | 6.70 | 7.30 | 23.56 | 0.58 | 22.43 | 24.69 |
| **Histologic Type (ICD-O-3)** | | | | | | | | | | | | | | | |
| Adenocarcinomas | 53.80 | 23.00 | <0.01 | 17.00 | <0.01 | 11.00 | <0.01 | 11.00 | 0.11 | 10.78 | 11.22 | 38.78 | 0.38 | 38.05 | 39.52 |
| Squamous cell neoplasia and other types (b) | 46.20 | 17.00 | <0.01 | 12.00 | <0.01 | 7.00 | <0.01 | 8.00 | 0.08 | 7.84 | 8.16 | 27.35 | 0.31 | 26.74 | 27.96 |
| **Sequence number** | | | | | | | | | | | | | | | |
| One primary only | 73.80 | 16.00 | <0.01 | 13.00 | <0.01 | 9.00 | <0.01 | 9.00 | 0.07 | 8.86 | 9.14 | 32.16 | 0.29 | 31.58 | 32.74 |
| 1st of 2 or more primaries | 5.30 | 50.00 | <0.01 | 39.00 | <0.01 | 22.00 | <0.01 | 47.00 | 1.60 | 43.87 | 50.13 | 74.67 | 1.30 | 72.12 | 77.22 |
| 2nd of 2 or more primaries | 16.90 | 16.00 | <0.01 | 12.00 | <0.01 | 6.00 | <0.01 | 9.00 | 0.16 | 8.69 | 9.32 | 27.94 | 0.51 | 26.95 | 28.93 |
| 3 or more primaries | 4.00 | 14.00 | <0.01 | 9.00 | <0.01 | 4.00 | <0.01 | 8.00 | 0.30 | 7.42 | 8.58 | 23.18 | 0.89 | 21.44 | 24.93 |
| **Summary stage** | | | | | | | | | | | | | | | |
| Localized | 20.10 | 40.00 | <0.01 | 32.00 | <0.01 | 21.00 | <0.01 | 23.00 | 0.50 | 22.03 | 23.97 | 61.16 | 0.70 | 59.79 | 62.54 |
| Regional | 47.60 | 22.00 | <0.01 | 16.00 | <0.01 | 9.00 | <0.01 | 12.00 | 0.12 | 11.77 | 12.23 | 35.08 | 0.38 | 34.34 | 35.82 |
| Distant | 32.40 | 6.00 | <0.01 | 4.00 | <0.01 | 2.00 | <0.01 | 5.00 | 0.06 | 4.89 | 5.11 | 13.43 | 0.23 | 12.98 | 13.88 |
| **Regional nodes positive** | | | | | | | | | | | | | | | |
| Lymph nodes not examined | 77.70 | 14.00 | <0.01 | 10.00 | <0.01 | 5.00 | <0.01 | 7.00 | 0.06 | 6.89 | 7.11 | 23.28 | 0.22 | 22.84 | 23.71 |
| Lymph nodes were negative | 12.10 | 58.00 | <0.01 | 48.00 | <0.01 | 33.00 | <0.01 | 56.00 | 1.67 | 52.73 | 59.27 | 91.21 | 1.07 | 89.12 | 93.30 |
| Lymph nodes were positive | 10.20 | 24.00 | <0.01 | 16.00 | <0.01 | 10.00 | <0.01 | 16.00 | 0.28 | 15.46 | 16.54 | 39.56 | 0.80 | 37.99 | 41.13 |

(*continued*)

**TABLE 2** | Continued

| | Percentage of total patients (%) | 3-year survival rate (%) | Probability density | 5-year survival rate (%) | Probability density | 10-year survival rate (%) | Probability density | Median survival time (months) | Standard Error | 95.0%, CI | | Mean survival time (months) | Standard Error | 95.0%, CI | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Lower | Upper | | | Lower | Upper |
| **Primary Site** | | | | | | | | | | | | | | | |
| C15.5-Lower third of esophagus | 56.50 | 23.00 | <0.01 | 17.00 | <0.01 | 11.00 | <0.01 | 11.00 | 0.10 | 10.81 | 11.19 | 37.94 | 0.36 | 37.24 | 38.65 |
| Other sites (c) | 43.50 | 17.00 | <0.01 | 12.00 | <0.01 | 7.00 | <0.01 | 8.00 | 0.09 | 7.83 | 8.17 | 27.51 | 0.33 | 26.87 | 28.16 |
| **Income** | | | | | | | | | | | | | | | |
| < $75,000 | 70.00 | 20.00 | <0.01 | 15.00 | <0.01 | 9.00 | <0.01 | 9.00 | 0.08 | 8.85 | 9.15 | 32.22 | 0.29 | 31.65 | 32.79 |
| $75,000+ | 30.00 | 22.00 | <0.01 | 16.00 | <0.01 | 10.00 | <0.01 | 11.00 | 0.14 | 10.74 | 11.26 | 36.26 | 0.48 | 35.32 | 37.19 |

*Note: (a) Other ethnicities included Asian, Pacific Islander and Native American/Native Alaskan.*

*(b) Other types included the histological types of esophageal cancer except for adenocarcinoma and squamous cell carcinoma.*

*(c) Others included C15.0-Cervical esophagus, C15.1-Thoracic esophagus, C15.2-Abdominal esophagus, C15.3-Upper third of esophagus, C15.4-Middle third of esophagus, C15.8-Overlapping lesion of esophagus and C15.9-Esophagus, NOS.*

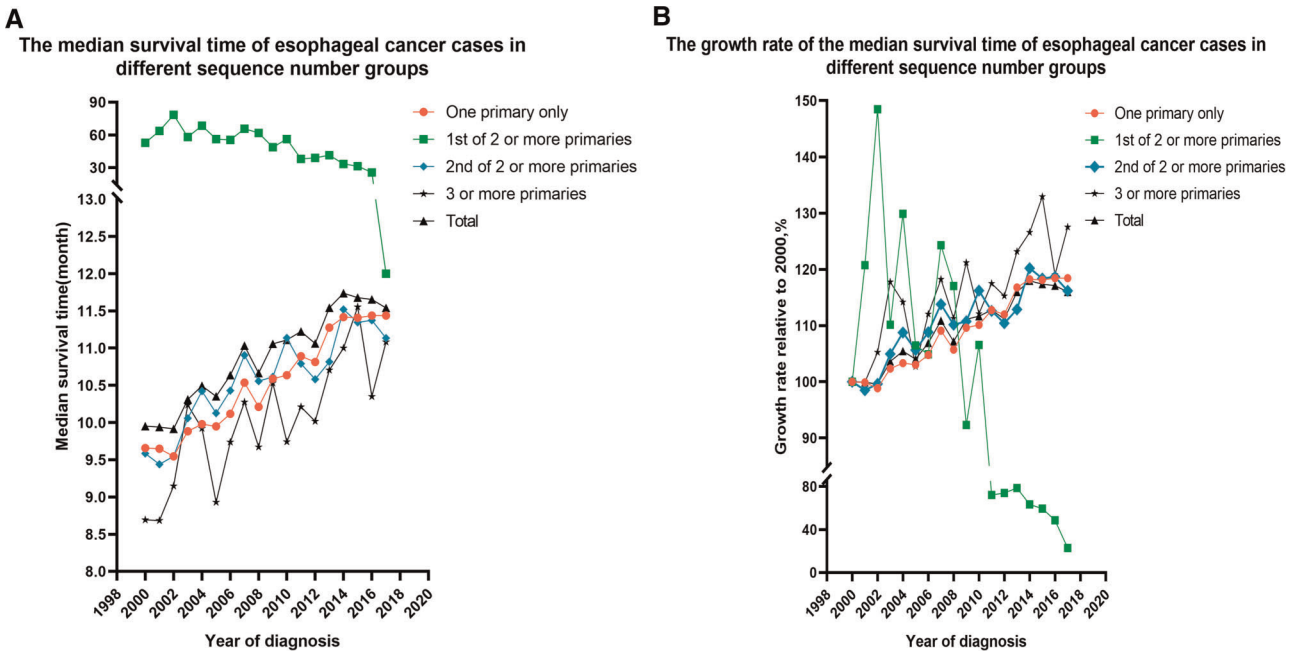


**FIGURE 1** | Changes to the median survival time and the growth rate of median survival time in patients with esophageal cancer from 2000 to 2017, according to the sequence number. (**A**) Changes in median survival time. (**B**) Changes in growth rate.

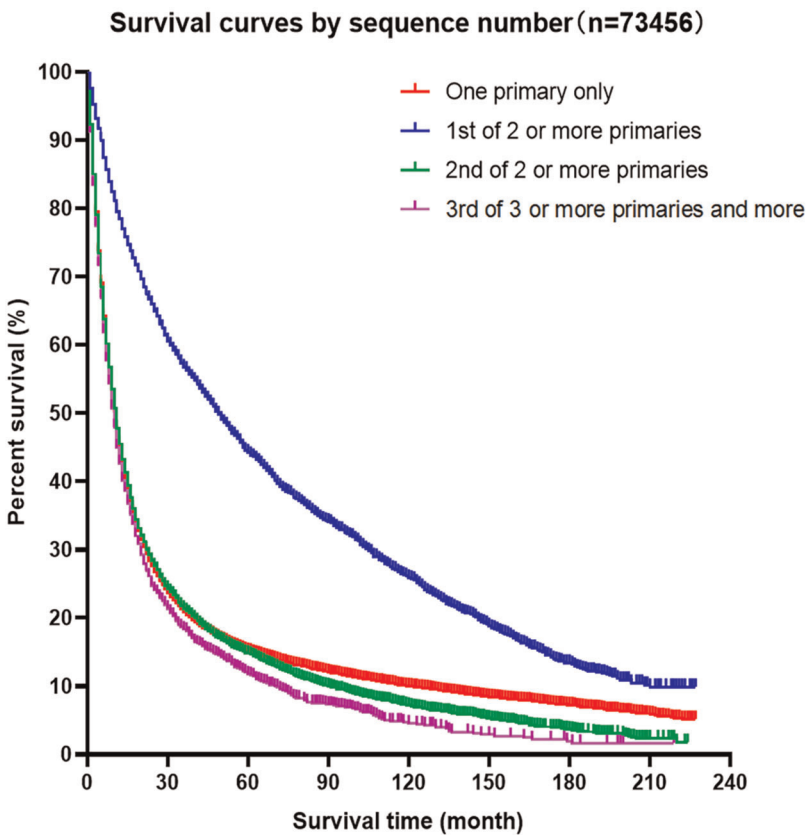


**FIGURE 2** | Kaplan–Meier survival curves for patients with esophageal cancer, according to sequence number.

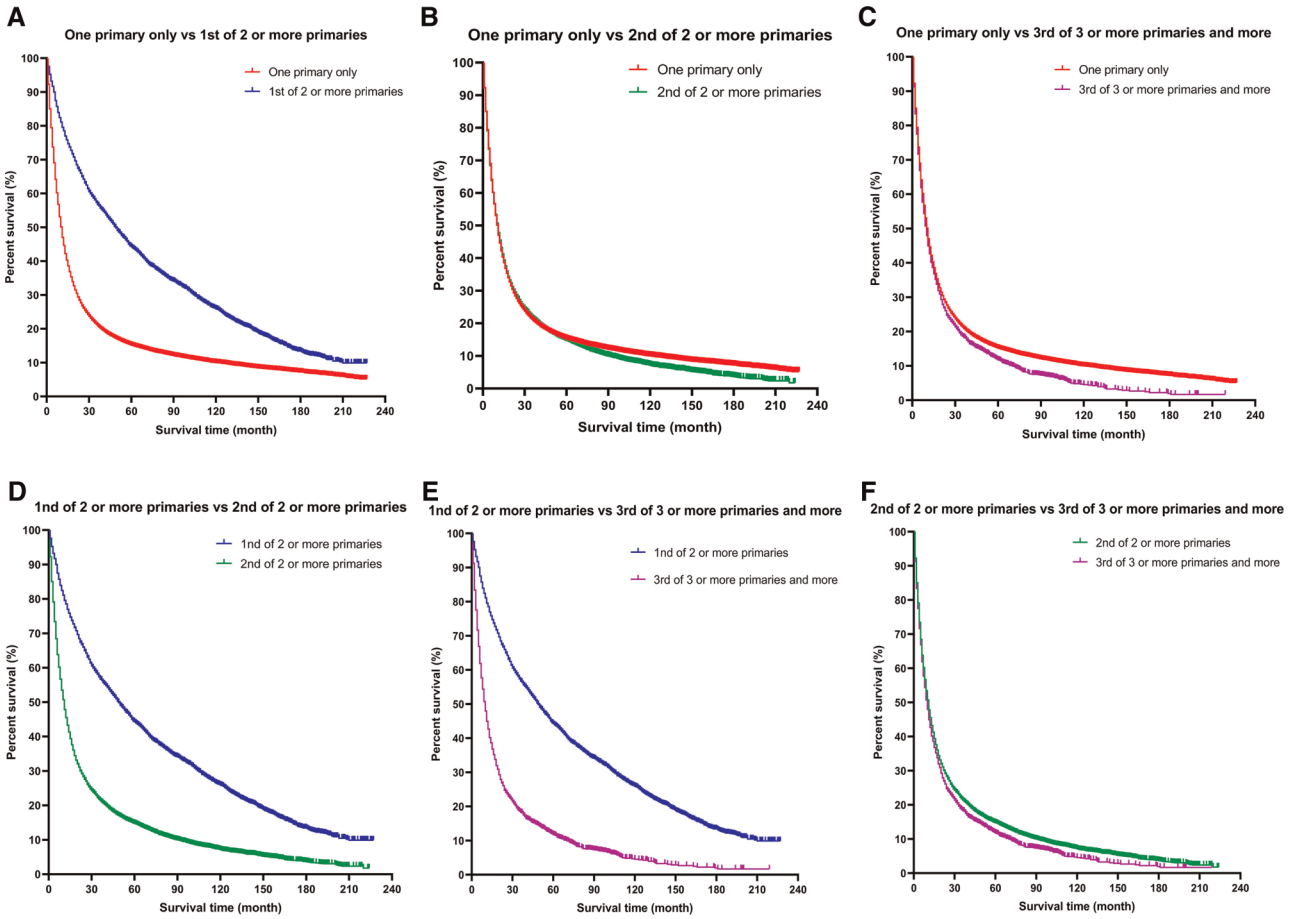


**FIGURE 3** | A more detailed classification based on the order of diagnosis of esophageal cancer among multiple primary cancers. (**A**) One primary only vs. 1st of two or more primaries. (**B**) One primary only vs. 2nd of two or more primaries. (**C**) One primary only vs. 3rd of three or more primaries. (**D**) 1st of two or more primaries vs. 2nd of two or more primaries. (**E**) 1st of two or more primaries vs. 3rd of three or more primaries. (**F**) 2nd of two or more primaries vs. 3rd of three or more primaries.

(HR = 1.16, 95% CI, 1.15–1.18), the black group (HR = 1.22, 95% CI, 1.19–1.25), the non-adenocarcinoma group (HR = 1.26, 95% CI, 1.24–1.28), the distant group (HR = 1.14, 95% CI, 1.12–1.17), the lymph node positive group (HR = 2.07, 95% CI, 2.00–2.15), the lymph node unexamined group (HR = 3.27, 95% CI, 3.18–3.37), and the other site group (HR = 1.13, 95% CI, 1.11–1.15) had higher risk of death ($p < 0.01$). The male group (HR = 0.99, 95% CI, 0.94–0.98), the regional group (HR = 0.77, 95% CI, 0.75–0.78), and the income $75,000 + group (HR = 0.97, 95% CI, 0.96–0.99) had a lower risk of death ($p < 0.05$) (**Table 4**).

## DISCUSSION

The development of surgical methods and advances in radiotherapy and chemotherapy technology have prolonged the survival time of patients with cancer. Studies have shown that patients with cancer have a higher risk of subsequent cancer than the general population (19–21). With the prolonged survival time of cancer survivors, the incidence of SPM has increased (22–26). Principles of management of multiple primary cancers are distinguished from common metastatic and recurrent cancers, and usually require comprehensive consideration from many aspects (27, 28). Therefore, the prognosis of patients with multiple primary cancers and the choice of treatment represent a new challenge for clinicians (3, 13). Previous studies analyzed the incidence rate (29, 30) of esophageal cancer and the survival rate (15, 16, 31–33) of patients with esophageal cancer. Although some preliminary explorations have been carried out, these studies had a short time span, a low amount of case data, the type of pathology was not described comprehensively, and the study methods were relatively simple. The follow-up data of esophageal cancer from the SEER database were updated in April 2021; therefore, it is necessary to conduct more in-depth studies on esophageal cancer combined with SPM based on the most recent data.

In many cancers, SPMs are considered a risk factor for poor prognosis. Research by Donin et al. showed that 1 out of 12 general cancer survivors suffer from SPM, and for patients

**TABLE 3** | Overall comparison and pairwise comparison of each group in Kaplan-Meier survival analysis.

| Comparison type | Comparative factor | Log Rank (Mantel-Cox) | | Breslow (Generalized Wilcoxon) | | Tarone-Ware | |
|---|---|---|---|---|---|---|---|
| | | Chi square | Significance | Chi square | Significance | Chi square | Significance |
| **Overall comparison** | Age | 2450.65 | <0.01 | 2391.85 | <0.01 | 2429.29 | <0.01 |
| | Race | 359.84 | <0.01 | 304.18 | <0.01 | 343.16 | <0.01 |
| | Histologic type (ICD-O-3) | 860.26 | <0.01 | 930.70 | <0.01 | 932.94 | <0.01 |
| | Sequence number | 1758.49 | <0.01 | 1929.31 | <0.01 | 2080.70 | <0.01 |
| | Summary stage | 9368.91 | <0.01 | 7634.22 | <0.01 | 8771.06 | <0.01 |
| | Regional nodes positive | 8002.74 | <0.01 | 8010.97 | <0.01 | 8521.65 | <0.01 |
| | Primary Site | 725.20 | <0.01 | 851.60 | <0.01 | 816.19 | <0.01 |
| | Income | 109.89 | <0.01 | 136.23 | <0.01 | 131.54 | <0.01 |
| **Pairwise comparison** | **Age** | | | | | | |
| | 75 + years vs. <75 years | 2450.65 | <0.01 | 2391.85 | <0.01 | 2429.30 | <0.01 |
| | **Race** | | | | | | |
| | Black vs. White and other races (a) | 359.84 | <0.01 | 304.18 | <0.01 | 343.16 | <0.01 |
| | **Histologic type (ICD-O-3)** | | | | | | |
| | Squamous cell neoplasia and other types (b) vs. Adenocarcinomas | 860.26 | <0.01 | 930.70 | <0.01 | 932.94 | <0.01 |
| | **Sequence number** | | | | | | |
| | 1st of 2 or more primaries vs. One primary only, 2nd of 2 or more primaries and 3 or more primaries | 1758.49 | <0.01 | 1929.31 | <0.01 | 2080.70 | <0.01 |
| | One primary only vs. 1st of 2 or more primaries | 1641.27 | <0.01 | 1888.85 | <0.01 | 2005.1 | <0.01 |
| | One primary only vs. 2nd of 2 or more primaries | 4.18 | 0.04 | 0.01 | 0.94 | 0.09 | 0.76 |
| | One primary only vs. 3 or more primaries | 22.82 | <0.01 | 8.75 | <0.01 | 12.46 | <0.01 |
| | 1st of 2 or more primaries vs. 2nd of 2 or more primaries | 1716.00 | <0.01 | 1717.49 | <0.01 | 1843.55 | <0.01 |
| | 1st of 2 or more primaries vs. 3 or more primaries | 1431.69 | <0.01 | 1406.65 | <0.01 | 1470.40 | <0.01 |
| | 2nd of 2 or more primaries vs. 3 or more primaries | 15.16 | <0.01 | 7.761 | <0.01 | 10.48 | <0.01 |
| | **Summary stage** | | | | | | |
| | Regional vs. Localized | 1491.63 | <0.01 | 1119.51 | <0.01 | 1369.08 | <0.01 |
| | Distant vs. Localized | 7900.62 | <0.01 | 5997.76 | <0.01 | 7111.73 | <0.01 |
| | Distant vs. Regional | 4756.79 | <0.01 | 4067.00 | <0.01 | 4589.46 | <0.01 |
| | **Regional nodes positive** | | | | | | |
| | Lymph nodes were negative vs. Lymph nodes not examined | 7162.58 | <0.01 | 6529.65 | <0.01 | 7278.61 | <0.01 |
| | Lymph nodes were positive vs. Lymph nodes not examined | 1178.81 | <0.01 | 1819.85 | <0.01 | 1628.48 | <0.01 |
| | Lymph nodes were positive vs. Lymph nodes were negative | 2031.43 | <0.01 | 1,870.28 | <0.01 | 2,041.87 | <0.01 |
| | **Primary Site** | | | | | | |
| | Other sites (c) vs. C15.5-Lower third of esophagus | 725.20 | <0.01 | 851.60 | <0.01 | 816.19 | <0.01 |
| | **Income** | | | | | | |
| | $75,000+ vs. <$75,000 | 109.89 | <0.01 | 136.23 | <0.01 | 131.54 | <0.01 |

*Note: (a) Other ethnicities included Asian, Pacific Islander and Native American/Native Alaskan.*
*(b) Other types included the histological types of esophageal cancer except for adenocarcinoma and squamous cell carcinoma.*
*(c) Others included C15.0-Cervical esophagus, C15.1-Thoracic esophagus, C15.2-Abdominal esophagus, C15.3-Upper third of esophagus, C15.4-Middle third of esophagus, C15.8-Overlapping lesion of esophagus and C15.9-Esophagus, NOS.*

with two types of cancer, 13% of patients died from initial cancer, but more than half (55%) died of SPM (22). Van lierde et al. showed that second primary tumors increased mortality significantly in patients with head and neck squamous cell carcinoma (34). Wu et al. showed that the prognosis of patients with SPM with non-small cell lung cancer is poor (35). Several studies have shown that the overall survival rate of patients with primary cancer of grade II or higher might be significantly lower than that of patients with grade I primary cancer I (36–39). However, the above conclusion might not be appropriate in patients with esophageal cancer. Nandy et al. believed that the survival rates of patients with esophageal cancer with or without SPM are similar (26). Some scholars believe that the main determinants of prognosis in patients with esophageal cancer complicated with SPM might be related to patient clinical factors (such as stage), but not the development of SPM. The conclusions of these studies differ from ours. This might reflect differences in research data sources and analysis methods such that the potential differences in the prognosis of the two groups of patients have not been revealed. Duchateau (4) showed that the prognosis of cancer survivors with SPMS is not necessarily very poor, which is similar to the conclusion of the present study. With the prognosis and active treatment of patients

**TABLE 4 |** Univariate Cox proportional hazards analysis of esophageal cancer based on the SEER database.

| Sub-group | Univariate analysis HR (95%CI) | *p*-value |
|---|---|---|
| **Sequence number** | | |
| One primary only | Reference (1) | |
| 1st of 2 or more primaries | 0.95 (0.92-0.99) | <0.01 |
| 2nd of 2 or more primaries | 0.98 (0.96-1.00) | <0.01 |
| 3 or more primaries | 0.93 (0.89-0.96) | <0.01 |
| **Age** | | |
| ≤74 years | Reference (1) | |
| 75+ years | 1.16 (1.15-1.18) | <0.01 |
| **Sex** | | |
| Female | Reference (1) | |
| Male | 0.96 (0.94-0.98) | <0.01 |
| **Race** | | |
| White and other races(a) | Reference (1) | |
| Black | 1.22 (1.19-1.25) | <0.01 |
| **Histologic type** | | |
| Adenocarcinomas | Reference (1) | |
| Squamous cell neoplasia and other types (b) | 1.26 (1.24-1.28) | <0.01 |
| **Summary stage** | | |
| Localized | Reference (1) | |
| Regional | 0.77 (0.75-0.78) | <0.01 |
| Distant | 1.14 (1.12-1.17) | <0.01 |
| **Regional nodes positive** | | |
| Lymph nodes were negative | Reference (1) | |
| Lymph nodes were positive | 2.07 (2.00-2.15) | <0.01 |
| Lymph nodes not examined | 3.27 (3.18-3.37) | <0.01 |
| **Primary Site** | | |
| Lower third of esophagus | Reference (1) | |
| other sites(c) | 1.13 (1.11-1.15) | <0.01 |
| **Household income** | | |
| <$75,000 | Reference (1) | |
| $75,000+ | 0.97 (0.96-0.99) | <0.01 |

*Note: (a) Other ethnicities included Asian, Pacific Islander and Native American/Native Alaskan.*
*(b) Other types included the histological types of esophageal cancer except for adenocarcinoma and squamous cell carcinoma.*
*(c) Others included C15.0-Cervical esophagus, C15.1-Thoracic esophagus, C15.2-Abdominal esophagus, C15.3-Upper third of esophagus, C15.4-Middle third of esophagus, C15.8-Overlapping lesion of esophagus and C15.9-Esophagus, NOS.*

with esophageal cancer with SPM receiving increased attention (5), the above-mentioned studies have obvious controversies and limitations (18, 35, 40, 41), and it is difficult to provide convincing, satisfactory, and consistent conclusions to help clinicians diagnose and treat these patients. Therefore, it is very important to conduct more in-depth research based on the updated large sample size of SEER data, the complete pathological types of esophageal cancer, and multiple analysis methods.

Through further analysis, we found that the median survival time of the EC-SPM group was longer. The Kaplan–Meier curve showed that the survival rate of esophageal cancer combined with SPM was higher, and univariate and multivariate Cox regression analysis results showed that the risk of death in the EC-SPM group was lower than that in the one primary malignancy only group. We considered that multiple surgeries, and repeated radiotherapy and chemotherapy might explain the better prognosis of patients with esophageal cancer with SPM compared with those without SPM. During the treatment of secondary cancer, frequent examination, radiotherapy, and chemotherapy might inhibit the recurrence and metastasis of esophageal cancer (13), thereby improving the overall curative effect. Patients with esophageal cancer usually present with an impaired immune ability, including an impaired complement activation pathway (42), while the treatment of second primary cancer might reactivate the immune system and exert antitumor effects (43). This interesting finding provides new insights and evidence for the need for further active treatment for esophageal cancer survivors with SPMs. In addition, our research showed that among cancer survivors, the survival rates of patients whose second primary cancer is esophageal cancer and patients with only esophageal cancer were statistically different. This differed from the results of some previous studies (36–39), and might have been caused by different data sources and statistical methods. However, this study is a retrospective study with a large sample size. In addition, multiple regression equation analysis of the Cox model was performed with multiple different models of variable adjustment, aiming to eliminate the interference of other covariates, which might have made our results more convincing.

Previous studies that carried out analysis of covariate in an identical way to that in the current study, e.g., Schlottmann et al., showed that surgical resection was rarely used in patients with esophageal adenocarcinoma who were aged 70 years or older in the United States (44). Moreover, Ruol et al. stated that old age should not be considered a contraindication for esophageal cancer surgery (45). The failure of older adults with esophageal cancer to receive surgery for their treatment perhaps explains the current finding of lower median survival times and growth rates among patients with esophageal cancer aged 75 years and older in the United States. Mariette et al. showed that one of the most important predictors of survival for patients with esophageal cancer is lymph node metastasis (46, 47). Less than one-third of patients in the United States and less than one-tenth of hospitals have fully checked the condition of the patients' lymph nodes (48). Our research showed that compared with patients with positive lymph node examinations, patients with esophageal cancer who have not undergone lymph node examination have a shorter median survival time. Therefore, improvement of the policies regarding lymph node examinations might reduce the risk of death for most patients with esophageal cancer.

The limitations of this study included the observation that those patients with positive lymph nodes had a better

**TABLE 5 |** Cox multiple regression equation analysis in different models of adjustment (total analysis and stratified analysis).

| Outcome | Model I HR (95%CI) *p*-value | Model II HR (95%CI) *p*-value | Model III HR (95%CI) *p*-value |
|---|---|---|---|
| **Total** | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.47 (0.45, 0.49) <0.01 | 0.47 (0.45, 0.48) <0.01 | 0.51 (0.49, 0.53) <0.01 |
| 2nd of 2 or more primaries | 1.02 (1.00, 1.05) <0.01 | 0.95 (0.93, 0.97) <0.01 | 1.00 (0.96 1.00) 0.04 |
| 3 or more primaries | 1.11 (1.07, 1.16) <0.01 | 1.00 (1.00, 1.04) 0.92 | 1.03 (0.99, 1.07) 0.17 |
| **Age** | | | |
| ≤74 years | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.46 (0.44, 0.49) <0.01 | 0.46 (0.44, 0.48) <0.01 | 0.50 (0.48, 0.52) <0.01 |
| 2nd of 2 or more primaries | 0.98 (0.95, 1.01) 0.16 | 0.98 (0.95, 1.01) 0.12 | 1.01 (0.98, 1.04) 0.61 |
| 3 or more primaries | 1.05 (0.99, 1.11) 0.14 | 1.05 (0.99, 1.12) 0.09 | 1.08 (1.02, 1.15) 0.01 |
| 75+ years | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.48 (0.45, 0.52) <0.01 | 0.48 (0.45, 0.52) <0.01 | 0.53 (0.49, 0.57) <0.01 |
| 2nd of 2 or more primaries | 0.92 (0.89, 0.95) <0.01 | 0.92 (0.89, 0.95) <0.01 | 0.95 (0.92, 0.98) <0.01 |
| 3 or more primaries | 0.96 (0.91, 1.01) 0.13 | 0.96 (0.91, 1.01) 0.14 | 0.99 (0.93, 1.05) 0.69 |
| **Sex** | | | |
| Female | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.46 (0.42, 0.50) <0.01 | 0.47 (0.43, 0.51) <0.01 | 0.50 (0.46, 0.54) <0.01 |
| 2nd of 2 or more primaries | 0.99 (0.95, 1.03) 0.66 | 0.96 (0.92, 1.00) <0.05 | 0.99 (0.95, 1.04) 0.67 |
| 3 or more primaries | 1.01 (0.94, 1.09) 0.71 | 0.96 (0.89, 1.03) 0.23 | 1.01 (0.94, 1.09) 0.82 |
| Male | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.47 (0.45, 0.49) <0.01 | 0.47 (0.45, 0.49) <0.01 | 0.52 (0.49, 0.54) <0.01 |
| 2nd of 2 or more primaries | 1.03 (1.01, 1.06) <0.01 | 0.95 (0.93, 0.98) <0.01 | 0.98 (0.96, 1.00) 0.10 |
| 3 or more primaries | 1.16 (1.10, 1.21) <0.01 | 1.02 (0.97, 1.08) 0.37 | 1.05 (1.00, 1.10) 0.08 |
| **Race** | | | |
| White and other races (a) | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.47 (0.45 0.49) <0.01 | 0.47 (0.45, 0.49) <0.01 | 0.52 (0.50, 0.54) <0.01 |
| 2nd of 2 or more primaries | 1.03 (1.01, 1.06) <0.01 | 0.95 (0.93, 0.98) <0.01 | 0.98 (0.96, 1.01) 0.15 |
| 3 or more primaries | 1.14 (1.09, 1.19) <0.01 | 1.01 (0.97, 1.05) 0.66 | 1.04 (0.99, 1.08) 0.10 |
| Black | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.45 (0.40, 0.50) <0.01 | 0.45 (0.41, 0.50) <0.01 | 0.47 (0.42, 0.52) <0.01 |
| 2nd of 2 or more primaries | 0.94 (0.89, 1.00) 0.06 | 0.91 (0.86, 0.97) <0.01 | 0.93 (0.88, 0.99) 0.03 |
| 3 or more primaries | 0.91 (0.80, 1.03) 0.15 | 0.88 (0.78, 1.00) 0.06 | 0.96 (0.84, 1.09) 0.51 |
| **Histologic type** | | | |
| Adenocarcinomas | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.47 (0.45, 0.50) <0.01 | 0.47 (0.44, 0.49) <0.01 | 0.55 (0.52, 0.58) <0.01 |
| 2nd of 2 or more primaries | 1.05 (1.02, 1.08) <0.01 | 0.94 (0.91, 0.97) <0.01 | 1.00 (0.97, 1.03) 0.84 |
| 3 or more primaries | 1.15 (1.08, 1.23) <0.01 | 0.98 (0.92, 1.05) 0.58 | 1.04 (0.97, 1.11) 0.24 |

(*continued*)

**TABLE 5** | Continued

| Outcome | Model I HR (95%CI) *p*-value | Model II HR (95%CI) *p*-value | Model III HR (95%CI) *p*-value |
|---|---|---|---|
| Squamous cell neoplasia and other types (b) | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.45 (0.43, 0.48) <0.01 | 0.46 (0.43, 0.48) <0.01 | 0.48 (0.46, 0.51) <0.01 |
| 2nd of 2 or more primaries | 0.97 (0.94, 1.00) <0.05 | 0.94 (0.91, 0.97) <0.01 | 0.96 (0.93, 0.99) <0.01 |
| 3 or more primaries | 1.01 (0.96, 1.06) 0.72 | 0.97 (0.92, 1.02) 0.25 | 1.02 (0.96, 1.07) 0.58 |
| **Summary stage** | | | |
| Localized | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.60 (0.56, 0.64) <0.01 | 0.60 (0.56, 0.64) <0.01 | 0.59 (0.549, 0.631) <0.01 |
| 2nd of 2 or more primaries | 1.20 (1.15, 1.26) <0.01 | 1.07 (1.02, 1.12) <0.01 | 1.02 (0.970, 1.065) 0.49 |
| 3 or more primaries | 1.48 (1.36, 1.60) <0.01 | 1.20 (1.11, 1.31) <0.01 | 1.11 (1.020, 1.200) <0.05 |
| Regional | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.51 (0.48, 0.54) <0.01 | 0.52 (0.488, 0.55) <0.01 | 0.51 (0.49, 0.54) <0.01 |
| 2nd of 2 or more primaries | 1.11 (1.07, 1.14) <0.01 | 1.01 (0.98, 1.05) 0.44 | 0.98 (0.95, 1.01) 0.13 |
| 3 or more primaries | 1.22 (1.15, 1.30) <0.01 | 1.08 (1.02, 1.14) <0.05 | 1.02 (0.96, 1.08) 0.61 |
| Distant | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.45 (0.42, 0.49) <0.01 | 0.45 (0.42, 0.49) <0.01 | 0.45 (0.41, 0.49) <0.01 |
| 2nd of 2 or more primaries | 1.05 (1.01, 1.09) <0.05 | 0.98 (0.94, 1.02) 0.31 | 0.97 (0.94, 1.01) 0.17 |
| 3 or more primaries | 1.09 (1.01, 1.18) <0.05 | 1.01 (0.93, 1.09) 0.90 | 1.00 (0.92, 1.08) 0.96 |
| **Regional nodes positive** | | | |
| Lymph nodes not examined | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.45 (0.43, 0.47) <0.01 | 0.45 (0.43, 0.47) <0.01 | 0.49 (0.47, 0.52) <0.01 |
| 2nd of 2 or more primaries | 0.95 (0.93, 0.97) <0.01 | 0.91 (0.89, 0.93) <0.01 | 0.96 (0.94 0.98) <0.01 |
| 3 or more primaries | 1.00 (0.95, 1.04) 0.82 | 0.94 (0.90, 0.98) <0.01 | 1.02 (0.97, 1.06) 0.48 |
| Lymph nodes were negative | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.67 (0.61, 0.74) <0.01 | 0.66 (0.60, 0.73) <0.01 | 0.69 (0.62, 0.6) <0.01 |
| 2nd of 2 or more primaries | 1.30 (1.20, 1.40) <0.01 | 1.19 (1.10, 1.29) <0.01 | 1.22 (1.13, 1.31) <0.01 |
| 3 or more primaries | 1.48 (1.26, 1.72) <0.01 | 1.33 (1.14, 1.56) <0.01 | 1.29 (1.11, 1.51) <0.01 |
| Lymph nodes were positive | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.50 (0.45, 0.56) <0.01 | 0.49 (0.440, 0.55) <0.01 | 0.49 (0.44, 0.55) <0.01 |
| 2nd of 2 or more primaries | 1.05 (0.97, 1.13) 0.24 | 0.99 (0.92, 1.06) 0.71 | 0.98 (0.91, 1.06) 0.65 |
| 3 or more primaries | 1.03 (0.87, 1.22) 0.71 | 0.94 (0.79, 1.11) 0.44 | 0.89 (0.75, 1.05) 0.17 |
| **Primary site** | | | |
| Lower third of esophagus | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.48 (0.45, 0.50) <0.01 | 0.47 (0.45, 0.50) <0.01 | 0.54 (0.51, 0.57) <0.01 |
| 2nd of 2 or more primaries | 1.05 (1.02, 1.09) <0.01 | 0.95 (0.92, 0.98) <0.01 | 1.01 (0.98, 1.04) 0.47 |
| 3 or more primaries | 1.16 (1.09, 1.23) <0.01 | 1.01 (0.95, 1.08) 0.69 | 1.10 (1.03, 1.17) <0.01 |

(*continued*)

**TABLE 5** | Continued

| Outcome | Model I HR (95%CI) *p*-value | Model II HR (95%CI) *p*-value | Model III HR (95%CI) *p*-value |
|---|---|---|---|
| Other sites (c) | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.45 (0.42, 0.47) <0.01 | 0.45 (0.42, 0.48) <0.01 | 0.48 (0.45, 0.51) <0.01 |
| 2nd of 2 or more primaries | 0.96 (0.93, 0.99) <0.01 | 0.93 (0.90, 0.95) <0.01 | 0.97 (0.94, 1.00) 0.08 |
| 3 or more primaries | 1.01 (0.95, 1.06) 0.81 | 0.95 (0.90, 1.01) 0.09 | 1.02 (0.96, 1.07) 0.61 |
| **Household income** | | | |
| ≤$75,000 | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.47 (0.45, 0.49) <0.01 | 0.47 (0.45, 0.49) <0.01 | 0.52 (0.49, 0.54) <0.01 |
| 2nd of 2 or more primaries | 1.02 (1.00, 1.05) 0.07 | 0.96 (0.93, 0.98) <0.01 | 0.98 (0.96, 1.01) 0.12 |
| 3 or more primaries | 1.12 (1.07, 1.17) <0.01 | 1.01 (0.96, 1.06) 0.74 | 1.03 (0.98, 1.08) 0.26 |
| $75,000+ | | | |
| One primary only | Reference (1) | Reference (1) | Reference (1) |
| 1st of 2 or more primaries | 0.46 (0.43, 0.50) <0.01 | 0.47 (0.44, 0.50) <0.01 | 0.51 (0.47, 0.54) <0.01 |
| 2nd of 2 or more primaries | 1.03 (0.99, 1.07) 0.12 | 0.94 (0.91, 0.98) <0.01 | 0.97 (0.94, 1.01) 0.17 |
| 3 or more primaries | 1.10 (1.03, 1.19) <0.01 | 0.98 (0.91, 1.06) 0.62 | 1.03 (0.96, 1.11) 0.42 |

*Note: (a) Other ethnicities included Asian, Pacific Islander and Native American/Native Alaskan.*
*(b) Other types included the histological types of esophageal cancer except for adenocarcinoma and squamous cell carcinoma.*
*(c) Others included C15.0-Cervical esophagus, C15.1-Thoracic esophagus, C15.2-Abdominal esophagus, C15.3-Upper third of esophagus, C15.4-Middle third of esophagus, C15.8-Overlapping lesion of esophagus, and C15.9-Esophagus, NOS. Result variable: Status. Exposure variable: Sequence number. Time variable: Survival months Model I is not adjusted. Model II was adjusted for age, sex, and ethnicity. Model III was adjusted for age, sex, ethnicity, histological type, summary stage, regional nodes positive, primary site, and household income.*

prognosis than those in the group without examined lymph nodes. This might have been because of the low rate of intraoperative assessment of lymph node status, a conclusion that is not strongly representative. Moreover, this study was a retrospective analysis; therefore, our conclusions need to be further verified by future prospective studies. According to the 2010 census, SEER 18 covers about 27.80% of the U.S. population. If we could obtain the whole esophageal cancer data, not limited to the United States, and include more covariates for analysis, our study will be more convincing. We hope to have more data for further research in the future.

## CONCLUSION

In conclusion, the overall survival of patients with cancer complicated with SPM is poor. However, the occurrence of the SPM in patients with esophageal cancer is not necessarily a risk factor for poor prognosis. This study provided new evidence and new ideas for future research on the pathophysiological mechanism and treatment concepts of esophageal cancer combined with SPM. These findings might provide valuable insights into aggressive treatment options and ongoing surveillance for SPM in esophageal cancer survivors and could help policymakers to monitor public health issues and implement interventions to reduce mortality from esophageal cancer.

## CONTRIBUTION TO THE FIELD STATEMENT

With the development of surgical techniques and advances in systemic treatments, the survival time of cancer survivors has increased; however, the chance of developing a second primary cancer has also increased. The overall survival rate of cancer survivors with second primary malignancies is poor. However, our study suggests that patients with esophageal cancer combined with second primary malignancies could have a better prognosis, and these patients might require more aggressive treatments. Our results provide new evidence and new ideas for future research on the pathophysiological mechanism and treatment concept of esophageal cancer combined with second primary malignant tumors.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

JYY, SH, JJX, and YPW contributed to the data collection, analysis, and writing of the manuscript. JYY, SH, WXZ, DYZ, YZ, DLY, JHP, JJX, and YPW contributed to the study design

and writing of the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This study was supported by grants from the National Natural Science Foundation of China (81860379 and 82160410), and the Science and Technology Planning Project at the Department of Science and Technology of Jiangxi Province, China (20171BAB 205075).

## ACKNOWLEDGMENTS

We hereby thank the participants for their time and effort during the data collection phase of the SEER project. We also thank the patients.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/article/10.3389/fsurg.2022.893429/full#supplementary-material.

## REFERENCES

1. Arnold M, Ferlay J, van Berge Henegouwen MI, Soerjomataram I. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. *Gut*. (2020) 69(9):1564–71. doi: 10.1136/gutjnl-2020-321600
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2021) 71(3):209–49. doi: 10.3322/caac.21660
3. Zhang G, Wu B, Wang X, Li J. Second primary malignancy in patients with esophageal adenocarcinoma and squamous cell carcinoma. *Medicine (Baltimore)*. (2019) 98(36):e17083. doi: 10.1097/md.0000000000017083
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. (2020) 70(1):7–30. doi: 10.3322/caac.21590
5. Nagasawa S, Onda M, Sasajima K, Takubo K, Miyashita M. Multiple primary malignant neoplasms in patients with esophageal cancer. *Dis Esophagus*. (2000) 13(3):226–30. doi: 10.1046/j.1442-2050.2000.00116.x
6. Kagei K, Hosokawa M, Shirato H, Kusumi T, Shimizu Y, Watanabe A, et al. Efficacy of intense screening and treatment for synchronous second primary cancers in patients with esophageal cancer. *Jpn J Clin Oncol*. (2002) 32(4): 120–7. doi: 10.1093/jjco/hyf028
7. Appelbaum R, Kuehler DC, Brodsky J. Pylorus Preserving Pancreaticoduodenectomy After Prior Esophagogastrectomy. *J Pancreat Cancer*. (2020) 6(1):116–8. doi: 10.1089/pancan.2020.0014
8. Jia H, Li Q, Yuan J, Sun X, Wu Z. Second primary malignancies in patients with colorectal cancer: a population-based analysis. *Oncologist*. (2020) 25(4): e644–50. doi: 10.1634/theoncologist.2019-0266
9. Waespe N, Belle FN, Redmond S, Schindera C, Spycher BD, Rössler J, et al. Cancer predisposition syndromes as a risk factor for early second primary neoplasms after childhood cancer - a national cohort study. *Eur J Cancer*. (2021) 145:71–80. doi: 10.1016/j.ejca.2020.11.042
10. Wei JL, Jiang YZ, Shao ZM. Survival and chemotherapy-related risk of second primary malignancy in breast cancer patients: a SEER-based study. *Int J Clin Oncol*. (2019) 24(8):934–40. doi: 10.1007/s10147-019-01430-0
11. DiMarzio P, Peila R, Dowling O, Timony DM, Balgobind A, Lee LN, et al. Smoking and alcohol drinking effect on radiotherapy associated risk of second primary cancer and mortality among breast cancer patients. *Cancer Epidemiol*. (2018) 57:97–103. doi: 10.1016/j.canep.2018.10.002
12. Zhu G, Chen Y, Zhu Z, Lu L, Bi X, Deng Q, et al. Risk of second primary cancer after treatment for esophageal cancer: a pooled analysis of nine cancer registries. *Dis Esophagus*. (2012) 25(6):505–11. doi: 10.1111/j.1442-2050.2011.01273.x
13. Chen D, Fan N, Mo J, Wang W, Wang R, Chen Y, et al. Multiple primary malignancies for squamous cell carcinoma and adenocarcinoma of the esophagus. *J Thorac Dis*. (2019) 11(8):3292–301. doi: 10.21037/jtd.2019.08.51
14. Li J, Ma J, Wang H, Niu J, Zhou L. Population-based analysis of small cell carcinoma of the esophagus using the SEER database. *J Thorac Dis*. (2020) 12(7):3529–38. doi: 10.21037/jtd-20-1428
15. Lin MQ, Li YP, Wu SG, Sun JY, Lin HX, Zhang SY, et al. Differences in esophageal cancer characteristics and survival between Chinese and Caucasian patients in the SEER database. *Onco Targets Ther*. (2016) 9:6435–44. doi: 10.2147/ott.S112038
16. Song Y, Wang W, Tao G, Zhu W, Zhou X, Pan P. Survival benefit of radiotherapy to patients with small cell esophagus carcinoma: an analysis of Surveillance Epidemiology and End Results (SEER) data. *Oncotarget*. (2016) 7(13):15474–80. doi: 10.18632/oncotarget.6764
17. Hildebrand P, Humke J, Oevermann E, Schloericke E, Bürk C, Roblick UJ, et al. Influence of second or multiple tumours on the prognosis of patients with colorectal cancer. *Acta Chir Iugosl*. (2012) 59(1):31–8. doi: 10.2298/aci1201031h
18. Duchateau CS, Stokkel MP. Second primary tumors involving non-small cell lung cancer: prevalence and its influence on survival. *Chest*. (2005) 127(4): 1152–8. doi: 10.1378/chest.127.4.1152
19. Joung JY, Kwon WA, Lim J, Oh CM, Jung KW, Kim SH, et al. Second primary cancer risk among kidney cancer patients in Korea: a population-based cohort study. *Cancer Res Treat*. (2018) 50(1):293–301. doi: 10.4143/crt.2016.543
20. Feller A, Matthes KL, Bordoni A, Bouchardy C, Bulliard JL, Herrmann C, et al. The relative risk of second primary cancers in Switzerland: a population-based retrospective cohort study. *BMC Cancer*. (2020) 20(1):51. doi: 10.1186/s12885-019-6452-0
21. Grundmann RT, Meyer F. [Second primary malignancy among cancer survivors - epidemiology, prognosis and clinical relevance]. *Zentralbl Chir*. (2012) 137(6):565–74. doi: 10.1055/s-0031-1283939
22. Donin N, Filson C, Drakaki A, Tan HJ, Castillo A, Kwan L, et al. Risk of second primary malignancies among cancer survivors in the United States, 1992 through 2008. *Cancer* (2016) 122(19):3075–86. doi: 10.1002/cncr.30164
23. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. (2015) 65(1):5–29. doi: 10.3322/caac.21254
24. de Moor JS, Mariotto AB, Parry C, Alfano CM, Padgett L, Kent EE, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol Biomarkers Prev*. (2013) 22(4):561–70. doi: 10.1158/1055-9965
25. Das A, Thomas S, Zablotska LB, Neugut AI, Chak A. Association of esophageal adenocarcinoma with other subsequent primary cancers. *J Clin Gastroenterol*. (2006) 40(5):405–11. doi: 10.1097/00004836-200605000-00008
26. Nandy N, Dasanu CA. Incidence of second primary malignancies in patients with esophageal cancer: a comprehensive review. *Curr Med Res Opin*. (2013) 29(9):1055–65. doi: 10.1185/03007995.2013.816276
27. Hu NC, Hsieh SC, Chen TJ, Chang JY. Multiple primary malignancies including colon, stomach, lung, breast, and liver cancer: a case report and literature review. *Chin Med J*. (2009) 122(24):3091–3. doi: 10.3760/cma.j.issn.0366-6999.2009.24.034
28. Hujala K, Sipilä J, Grenman R. Panendoscopy and synchronous second primary tumors in head and neck cancer patients. *Eur Arch Otorhinolaryngol*. (2005) 262(1):17–20. doi: 10.1007/s00405-004-0743-y
29. Dubecz A, Solymosi N, Stadlhuber RJ, Schweigert M, Stein HJ, Peters JH. Does the incidence of adenocarcinoma of the esophagus and gastric cardia continue to rise in the twenty-first century?-a SEER database analysis. *J Gastrointest Surg*. (2013. doi: 10.1007/s11605-013-2345-8
30. Coleman HG, Xie SH, Lagergren J. The epidemiology of esophageal adenocarcinoma. *Gastroenterology*. (2018) 154(2):390–405. doi: 10.1053/j.gastro.2017.07.046
31. Kukar M, Groman A, Malhotra U, Warren GW, Bogner P, Nwogu CE, et al. Small cell carcinoma of the esophagus: a SEER database analysis. *Ann Surg Oncol*. (2013) 20(13):4239–44. doi: 10.1245/s10434-013-3167-3

32. Xiao Q, Xiao H, Ouyang S, Tang J, Zhang B, Wang H. Primary small cell carcinoma of the esophagus: comparison between a Chinese cohort and Surveillance, Epidemiology, and End Results (SEER) data. *Cancer Med*. (2019) 8(3):1074–85. doi: 10.1002/cam4.2001
33. Pucher PH, Rahman SA, Walker RC, Grace BL, Bateman A, Iveson T, et al. Outcomes and survival following neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus: Inverse propensity score weighted analysis. *Eur J Surg Oncol*. (2020) 46(12): 2248–56. doi: 10.1016/j.ejso.2020.06.038
34. Van Lierde C, Gyselinck B, Meulemans J, Bisschops R, Delaere P, Vander Poorten V. The value of virtual chromoendoscopy in the workup of patients with head and neck squamous cell carcinoma. *Curr Oncol Rep*. (2020) 22(12):121. doi: 10.1007/s11912-020-00982-z
35. Wu B, Cui Y, Tian J, Song X, Hu P, Wei S. Effect of second primary cancer on the prognosis of patients with non-small cell lung cancer. *J Thorac Dis*. (2019) 11(2):573–82. doi: 10.21037/jtd.2018.11.96
36. Al-Husseini MJ, Saad AM, Mohamed HH, Alkhayat MA, Sonbol MB, Abdel-Rahman O. Impact of prior malignancies on outcome of colorectal cancer; revisiting clinical trial eligibility criteria. *BMC Cancer*. (2019) 19(1):863. doi: 10.1186/s12885-019-6074-6
37. Bian X, Xia J, Wang K, Wang Q, Yang L, Wu W, et al. The effects of a prior malignancy on the survival of patients with ovarian cancer: a population-based study. *J Cancer*. (2020) 11(21):6178–87. doi: 10.7150/jca.46584
38. Lin C, Wu J, Ding S, Goh C, Andriani L, Shen K, et al. Impact of prior cancer history on the clinical outcomes in advanced breast cancer: a propensity score-adjusted, population-based study. *Cancer Res Treat*. (2020) 52(2): 552–62. doi: 10.4143/crt.2019.210
39. Zhou H, Huang Y, Qiu Z, Zhao H, Fang W, Yang Y, et al. Impact of prior cancer history on the overall survival of patients newly diagnosed with cancer: a pan-cancer analysis of the SEER database. *Int J Cancer*. (2018) 143(7):1569–77. doi: 10.1002/ijc.31543
40. Manavoğlu O, Orhan B, Evrensel T, Karabulut Y, Ozkocaman V, Ozyardimci C. Second primary cancer due to radiotherapy and chemotherapy. *J Environ Pathol Toxicol Oncol*. (1996) 15(2–4):275–8.
41. Otowa Y, Nakamura T, Takiguchi G, Yamamoto M, Kanaji S, Imanishi T, et al. Safety and benefit of curative surgical resection for esophageal squamous cell cancer associated with multiple primary cancers. *Eur J Surg Oncol*. (2016) 42(3):407–11. doi: 10.1016/j.ejso.2015.11.012
42. Verma A, Matta A, Shukla NK, Deo SV, Gupta SD, Ralhan R. Clinical significance of mannose-binding lectin-associated serine protease-2 expression in esophageal squamous cell carcinoma. *Int J Cancer*. (2006) 118(12):2930–5. doi: 10.1002/ijc.21721
43. Reisländer T, Groelly FJ, Tarsounas M. DNA damage and cancer immunotherapy: a STING in the tale. *Mol Cell*. (2020) 80(1):21–8. doi: 10.1016/j.molcel.2020.07.026
44. Schlottmann F, Strassle PD, Molena D, Patti MG. Influence of patients' age in the utilization of esophagectomy for esophageal adenocarcinoma. *J Laparoendosc Adv Surg Tech A*. (2019) 29(2):213–7. doi: 10.1089/lap.2018.0434
45. Ruol A, Portale G, Zaninotto G, Cagol M, Cavallin F, Castoro C, et al. Results of esophagectomy for esophageal cancer in elderly patients: age has little influence on outcome and survival. *J Thorac Cardiovasc Surg*. (2007) 133(5):1186–92. doi: 10.1016/j.jtcvs.2006.12.040
46. Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. *Ann Surg*. (2008) 247(2):365–71. doi: 10.1097/SLA.0b013e31815aaadf
47. Hofstetter W, Correa AM, Bekele N, Ajani JA, Phan A, Komaki RR, et al. Proposed modification of nodal status in AJCC esophageal cancer staging system. *Ann Thorac Surg*. (2007) 84(2):365–73; discussion 74-5. doi: 10.1016/j.athoracsur.2007.01.067
48. Merkow RP, Bilimoria KY, Chow WB, Merkow JS, Weyant MJ, Ko CY, et al. Variation in lymph node examination after esophagectomy for cancer in the United States. *Arch Surg*. (2012) 147(6):505–11. doi: 10.1001/archsurg.2011.2215


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Surgery

CASE REPORT
published: 31 May 2022
doi: 10.3389/fsurg.2022.893259

# Case Report: Primary Hyperparathyroidism due to Posterior Mediastinal Parathyroid Adenoma With One-Year Follow-Up

*Yi Shao[1], Qingdong Zeng[1], Bin Lv[1], Xu Chen[2] and Lei Sheng[1]**

*[1]Department of Thyroid Surgery, General Surgery, Qilu Hospital of Shandong University, Jinan, China, [2]Department of Pathology, Qilu Hospital of Shandong University, Jinan, China*

Ectopic parathyroid adenoma, though rare, is one of the causes of persistent hyperparathyroidism and recurrence of hyperparathyroidism. Ectopic parathyroid glands can be seen in thymus, thyroid, and mediastinum. However, ectopic parathyroid adenoma occurred in the posterior superior mediastinum is extremely rare. Here, we report a case of primary hyperparathyroidism caused by ectopic parathyroid adenoma located in the posterior superior mediastinum. Serum parathyroid hormone, calcium, and vitamin D levels of the patient was followed up for one year.

**Keywords: ectopic parathyroid adenoma, primary hyperparathyroidism, posterior superior mediastinum, thoracic surgery, vitamin D deficiency**

OPEN ACCESS

***Edited by:***
*Nuria Maria Novoa, University of Salamanca Health Care Complex, Spain*

***Reviewed by:***
*Federico Cappellacci, University of Cagliari, Policlinico Universitario Duilio Casula, Italy*
*Coskun Meric, University of Health Sciences, Turkey*

***Correspondence:**
*Lei Sheng*
*lei.sheng@sdu.edu.cn*

***Specialty section:***
*This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery*

***Received:*** *09 March 2022*
***Accepted:*** *10 May 2022*
***Published:*** *31 May 2022*

***Citation:***
*Shao Y, Zeng Q, Lv B, Chen X and Sheng L (2022) Case Report: Primary Hyperparathyroidism due to Posterior Mediastinal Parathyroid Adenoma With One-Year Follow-Up. Front. Surg. 9:893259. doi: 10.3389/fsurg.2022.893259*

## INTRODUCTION

Primary hyperparathyroidism (PHPT) is a disease characterized by an excessive secretion of parathyroid hormone, leading to osteoporosis, ureteral calculi, and serum hypercalcemia. Ninety percent of parathyroid cases were caused by a single parathyroid adenoma, and the less common causes included multiple hyperplasia of the gland (6%), double adenoma (4%), and parathyroid carcinoma (<1%) (1). In about 6–16% of cases, one or more hyperparathyroidism adenoma is located in the ectopic position (2). Mediastinum is less common as an ectopic site, accounting for 1–2% of the cases (3). Among mediastinal ectopic parathyroid gland adenoma, posterior mediastinal ectopic parathyroid gland adenoma was extremely rare in literature reports. Here, we reported a case of PHPT due to posterior mediastinal ectopic parathyroid gland adenoma with one-year follow-up.

## CASE DESCRIPTION

### Patient Information

A 46-year-old female patient had a history of elevated alkaline phosphatase (AKP) for 4 years. She had occasional thirst, with no abdominal pain, abdominal distension, acid reflux, heartburn, constipation, dyspepsia, or nocturia. The history of renal insufficiency was denied. The patient had regular physical examination every year and found that his AKP level increased

progressively. Osteoporosis was found by physical examination two years ago with no bone pain or fracture history. The patient's menstruation is still regular, and there is no obvious history of dysmenorrhea.

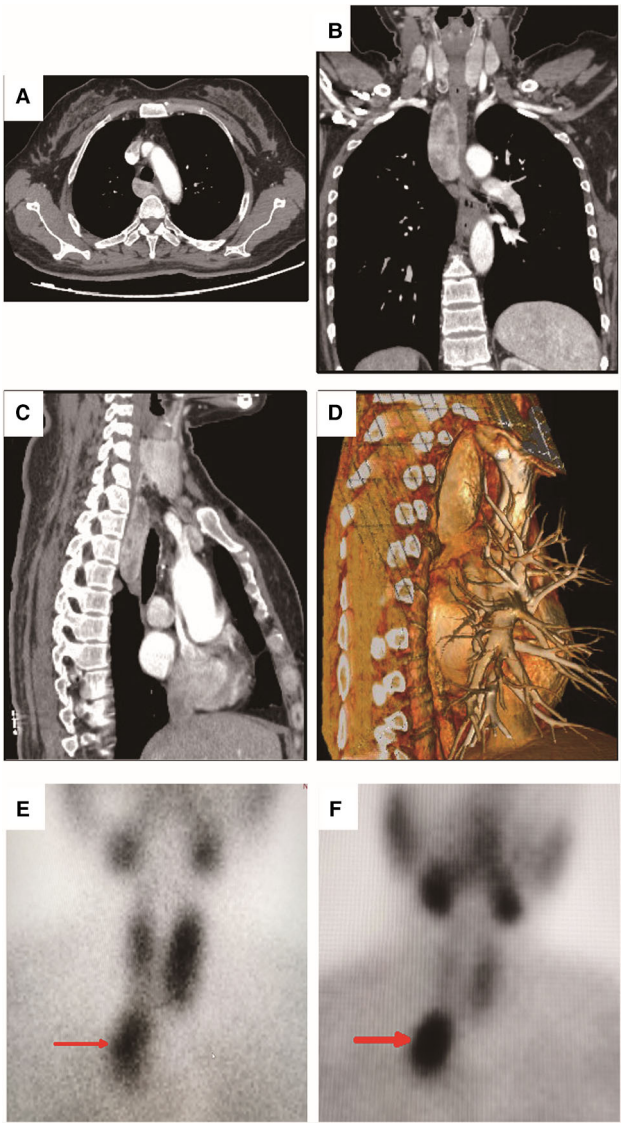


**FIGURE 1 | Computed tomography (CT) scan and $99^{m}$-Technetium sestamibi scanning of the patient.** (**A**) Transverse view of the CT scanning showed a mixed density mass with uneven enhancement in the posterior mediastinum. The maximum cross-section size was about 3.3×1.9 cm.; (**B**) Coronal view of the CT scanning; (**C**) Sagittal view of the CT scanning; (**D**). Three-dimensional reconstruction in sagittal view of the CT scanning; (**E**) The 15th minute static imaging: the left thyroid lobe was more prominent, whereas the uptake of imaging agent in the right thyroid lobe was decreased; In addition, localized abnormal uptake of imaging agent under the right thyroid lobe was found (as shown by the red arrow). (**F**) The two-hour delayed imaging: the uptake of thyroid imaging was lower than that before, the abnormal imaging agent concentration under the right thyroid lobe was clearly displayed (as shown by the red arrow).

## Diagnostic Assessment

Blood test results one month before operation showed that AKP was 294 U/L (normal range 30–100 U/L), PTH 981.20 pg/mL (normal range 15–65 pg/mL), calcium 2.93 mmol/L (normal range 2.00–2.60 mmol/L), phosphorus 0.64 mmol/L, Vitamin D 6.97 ng/mL (normal range ≥30 ng/mL). Right forearm bone mineral density detection showed BMD 0.391, Z score −5.33, and t score −5.44. Computed tomography scan showed posterior superior mediastinal was occupied with a cystic solid tumor whose maximum cross-section size was about 3.3 × 1.9 cm (**Figure 1A–1D**). No special signs were found by neck ultrasound. The patient underwent 99mTechnetium sestamibi scanning, indicating a mass with increased uptake of imaging agent in the posterior mediastinum (**Figure 1E–1F**).

## Therapeutic Intervention

The patient had daily subcutaneous injection of a total amount of 100–300 IU per day of salmon calcitonin preoperatively due to hypercalcemia and underwent single-port thoracoscopic resection of the mediastinal tumor. The tumor was carefully removed by ultrasonic scalpel. The volume of the tumor was about 6.0 × 4.2 × 1.0 cm at pathological examination. Postoperative pathology confirmed parathyroid adenoma (**Figure 2**).

## Follow-up and Outcomes

The PTH and blood calcium levels decreased instantly after the operation. The PTH level on the first day after the operation was 93.96 pg/mL, and on the second day after the operation was 7.29 pg/mL. However, on the fourth day after the operation, the PTH level raised to 65.61 pg/mL (normal range 15–65 pg/mL) and continued to rise to 159.2 pg/mL one month after

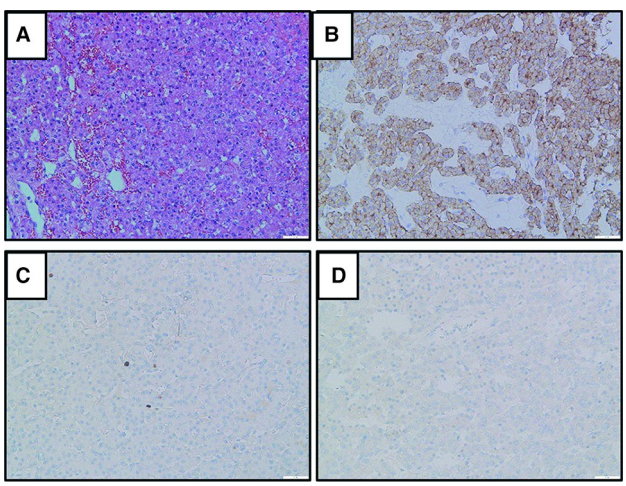


**FIGURE 2 | Histology and immunohistochemistry of parathyroid adenoma.** (**A**). Hematoxylin and eosin staining. (**B**) Positivity for parathyroid hormone. (**C**) About 2% of positivity for Ki-67 staining. (**D**) Negativity for thyroid transcription factor 1 (TTF-1). Magnification ×200.

the operation. Serum calcium concentration was still within the normal level and no specific symptoms were shown. Meanwhile, the vitamin D level was found lower than the normal level in the first month after surgery. So the patient was supplemented with vitamin D 800 IU per day. The PTH level continues to decrease, whereas vitamin D levels continue to rise ever since exogenous vitamin D was supplemented. One year after the operation, serum PTH, calcium, and vitamin D levels returned to normal (**Figure 3**).

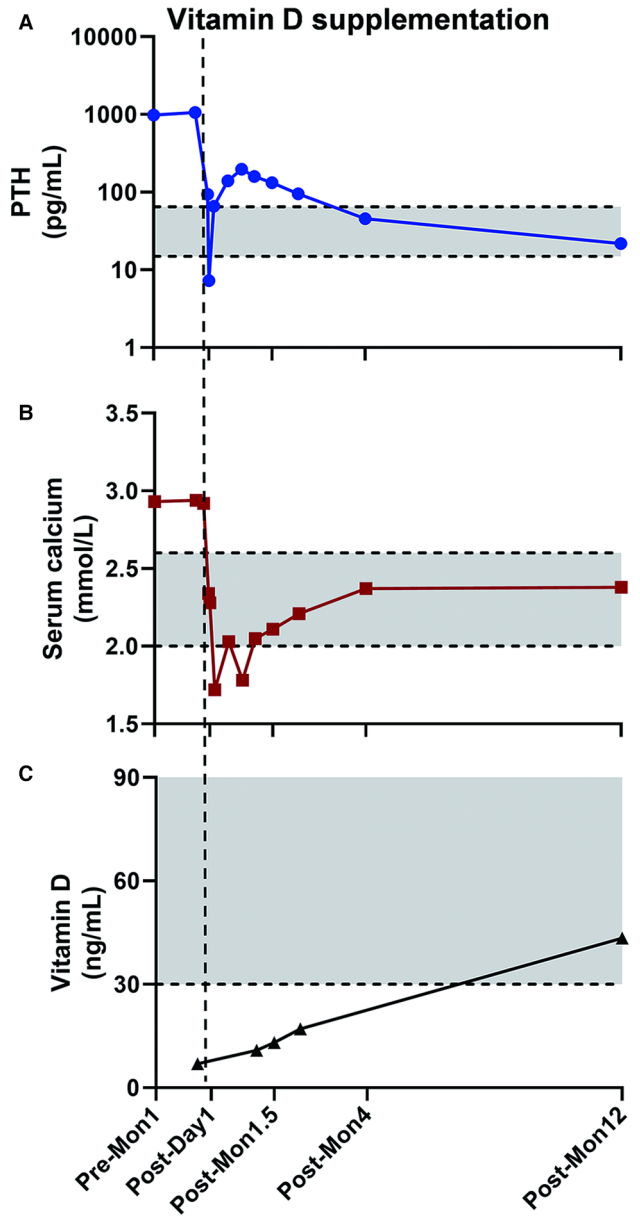


**FIGURE 3 | The PTH, serum calcium, and Vitamin D level changed perioperatively.** Grey area was the normal range PTH (15–65 pg/mL), serum calcium (2.00–2.60 mmol/L), and Vitamin D level (≥30 ng/mL) defined at our center. The PTH level decreased immediately after the operation but went up at the early follow-up (**A**), while the postoperative blood calcium level was lower than the upper limit of normal value (**B**). After vitamin D levels were normalized with vitamin D supplementation (**C**), the PTH level went back to normal level at the one year of follow-up. Pre-Mon 1: one month prior to surgery. Post-Day 1: one day after surgery. Post-Mon 1.5, Post-Mon 4, and Post-Mon 12: 1.5, 4, and 12 months after surgery.

## Timeline

The timeline of clinical interventions for this patient was shown in **Figure 4**.

## DISCUSSION

PHPT is a very common endocrine disease characterized by inappropriate secretion of parathyroid hormone in the absence of external stimulation. 80%–95% of patients with PHPT can be cured by parathyroidectomy after the first operation (4). Patients who were not cured had hypercalcemia immediately after operation, or hypercalcemia after long-term normal blood calcium level. The failure of parathyroidectomy is mainly due to inadequate resection of parathyroid adenoma or the presence of a second adenoma, parathyroid hyperplasia (usually with familial PHPT syndrome), or parathyroid carcinoma. A common and main reason for persistent PHPT is the ectopic location of the parathyroid, which is the result of abnormal migration of the parathyroid in early fetal development (5).

The parathyroid glands originate from the endoderm and develop from the dorsal wing of the third and fourth pharyngeal pouch (6). Embryologically, the upper parathyroid originates from the fourth-gill sac and migrates caudally with the thyroid gland, while the lower parathyroid originates from the third-gill sac and migrates with the thymus gland. The distribution area of the superior parathyroid gland is narrow, and it is stably distributed in the fat tissue around the thyroid gland, near the route of the recurrent laryngeal nerve until it enters the cricothyroid muscle. On the contrary, the inferior

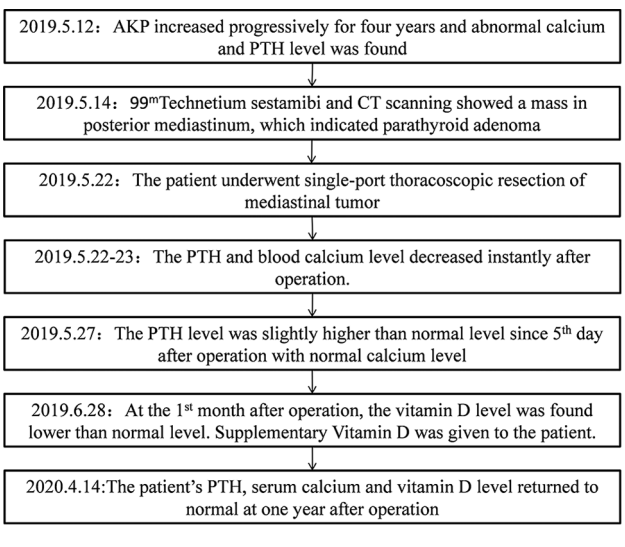


**FIGURE 4 | The timeline of clinical interventions of this patient.**

parathyroid gland is distributed in a wide area of thyrothoracic ligament and pretracheal fat tissue, around the lower pole of the thyroid gland (6, 7). Autopsy confirms that the incidence of ectopic parathyroid is between 2% and 42.8% (8, 9). Ectopic parathyroid adenomas may be located anywhere from the base of the tongue to the mediastinum. The most common location of ectopic lower parathyroid is in the anterior mediastinum, which is related to thymus or thyroid, while the most common location of ectopic upper parathyroid is in tracheoesophageal sulcus and posterior esophagus (10, 11). Posterior superior mediastinum is a rare ectopic location of the superior parathyroid gland (10), which was rarely reported in the literature.

In suspected cases of ectopic parathyroid adenoma, neck ultrasound (US) and 99mTechnetium sestamibi scanning (MIBI) are the preferred imaging methods. The US can effectively detect the adenoma around the lower pole of the thyroid, but it is not effective to show the ectopic parathyroid adenoma in the posterior or upper mediastinum (12). Ectopic parathyroid can be detected by MIBI with the sensitivity almost the same as that of *in situ* parathyroid adenoma (13). In most studies, the sensitivity of ultrasound alone as a single method to identify ectopic adenoma was 27–89%, while MIBI alone was 80–90% (14–16).

For patients with posterior superior mediastinal ectopic parathyroid adenoma, video-assisted thoracoscopy (VATS) combined with intraoperative MIBI scan and parathyroid hormone assessment can minimize the surgical anatomy and avoid median sternotomy and thoracotomy. It has been suggested that parathyroid hormone levels should be assessed within 15 min after parathyroidectomy, and should be reduced to at least 50% of that before operation. If PTH continues to be higher than normal, ectopic or multiglandular disease is suspected (17). However, the definition of curative parathyroidectomy is: blood calcium is normal 6 months after the operation, and the definition of recurrence of hyperparathyroidism is: hypercalcemia caused by hyperparathyroidism occurs again 6 months after blood calcium is normal (18). Wang found that in 50% of the patients whose parathyroid adenoma had been successfully removed, blood calcium decreased by 2–3 mg in the first 24 h after surgery. Unless bone starvation syndrome occurs, the initial decrease in blood calcium can be restored 3–4 days after surgery and the blood calcium is within the normal range (19). In patients with high serum AKP level and osteoporosis before the operation, bone starvation syndrome and lower-than-expected blood calcium level may appear after the operation. This is consistent with the patient's condition. Under normal circumstances, parathyroid hormone should be decreased after successful parathyroid surgery. However, abnormally high PTH level with normal calcium level after the operation can be seen in certain percentage of patients whose parathyroid adenoma have successfully been removed, accounting for 8%–43% of patients (20–22). 78%–88% of the patients with elevated postoperative PTH levels can eventually decrease to normal range or lower within 12–16 months. However, some reports showed that PTH level could still be elevated, with normal blood calcium level, 1–4 years after operation (23, 24).

Abnormally high postoperative PTH level is more common in the following cases: ① Severe preoperative hyperparathyroidism (such as higher PTH level, larger glands, and multiple gland diseases); ② Decreased sensitivity of peripheral tissue to PTH (possibly due to chronic long-term increase of PTH before operation); ③ Renal insufficiency; ④ Exaggerated reflection of excessive decalcification of bone after operation; and ⑤Preoperative vitamin D deficiency. Vitamin D deficiency is more common in elderly patients and female patients (20, 23, 24). Therefore, for most patients, higher postoperative PTH does not mean the failure of surgery, nor is it a good indicator of postoperative disease status. Charlett reported that the sensitivity and specificity of abnormal serum PTH level to predict surgical failure were 62.1% and 75%, respectively (25). Some researchers suggested that detection of PTH level in patients with PHPT after surgery may mislead the treatment. For patients with normal blood calcium, PTH monitoring is not essential (26). Others recommended that the blood calcium level should be reexamined regularly after the operation, but not PTH. If PTH is detected and higher than normal level, then vitamin D level should also be detected in case of existence of vitamin D deficiency (25, 26).

In this case, vitamin D deficiency may be the cause of elevated PTH levels. Vitamin D in circulation binds with vitamin D binding protein, transports to liver, and generates 25 hydroxyvitamin [25–(OH) $D_3$] under the action of 25 hydroxylase. 25–(OH) $D_3$ is the main form of vitamin D in human blood circulation with no biological activity, and it is transformed into 1, 25–(OH) $_2D_3$, the active form of vitamin D, under the action of 1α-hydroxylase in kidney. 1, 25–(OH) $_2D_3$ can reduce PTH synthesis and secretion through negative feedback. On the contrary, the parathyroid hormone can increase the renal tubular reabsorption of calcium and promote the renal production of 1, 25–(OH) $_2D_3$, and promote the conversion of 25–(OH) $D_3$ to 1, 25–(OH) $_2D_3$ (27). In this case, the vitamin D deficiency before operation and the failure of early exogenous supplementation may be the main reason for the sustained elevation of PTH level after the operation. After vitamin D was supplemented, the PTH level of this patient gradually returned to normal, which also verified our conjecture. In addition, we speculated that the long history of abnormally high PTH level may cause decreased sensitivity to PTH in peripheral tissue, which is plausibly a contributing factor for increased postoperative PTH level.

## DATA AVAILABILITY STATEMENT

The original data presented in the study are included in the article, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

The authors that contributed to the conception and design of the study were YS, QZ, and LS. Data acquisition and interpretation were performed by YS, CX, and LS. The first draft of the manuscript was written by YS. All authors contributed to the article and approved the submitted version.

## REFERENCES


1. Ruda JM, Hollenbeak CS, Stack Jr BC. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg*. (2005) 132(3):359–72. doi: 10.1016/j.otohns.2004.10.005
2. Roy M, Mazeh H, Chen H, Sippel RS. Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients. *World J Surg*. (2013) 37(1):102–6. doi: 10.1007/s00268-012-1773-z
3. Amer K, Khan AZ, Rew D, Lagattolla N, Singh N. Video assisted thoracoscopic excision of mediastinal ectopic parathyroid adenomas: a UK regional experience. *Ann Cardiothorac Surg*. (2015) 4(6):527–34. doi: 10.3978/j.issn.2225-319X.2015.09.04
4. Marcocci C, Cetani F. Clinical practice: primary hyperparathyroidism. *N Engl J Med*. (2011) 365(25):2389–97. doi: 10.1056/NEJMcp1106636
5. Kelly HR, Hamberg LM, Hunter GJ. 4D-CT for preoperative localization of abnormal parathyroid glands in patients with hyperparathyroidism: accuracy and ability to stratify patients by unilateral versus bilateral disease in surgery-naive and re-exploration patients. *AJNR Am J Neuroradiol*. (2014) 35(1):176–81. doi: 10.3174/ajnr.A3615
6. Mohebati A, Shaha AR. Anatomy of thyroid and parathyroid glands and neurovascular relations. *Clin Anat*. (2012) 25(1):19–31. doi: 10.1002/ca.21220
7. Fancy T, Gallagher 3rd D, Hornig JD. Surgical anatomy of the thyroid and parathyroid glands. *Otolaryngol Clin North Am*. (2010) 43(2):221–7. doi: 10.1016/j.otc.2010.01.001
8. Wang C. The anatomic basis of parathyroid surgery. *Ann Surg*. (1976) 183(3):271–5. doi: 10.1097/00000658-197603000-00010
9. Hojaij F, Vanderlei F, Plopper C, Rodrigues CJ, Jacomo A, Cernea C, et al. Parathyroid gland anatomical distribution and relation to anthropometric and demographic parameters: a cadaveric study. *Anat Sci Int*. (2011) 86(4):204–12. doi: 10.1007/s12565-011-0111-0
10. Phitayakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. *Am J Surg*. (2006) 191(3):418–23. doi: 10.1016/j.amjsurg.2005.10.049
11. Mendoza V, Ramirez C, Espinoza AE, Gonzalez GA, Pena JF, Ramirez ME, et al. Characteristics of ectopic parathyroid glands in 145 cases of primary hyperparathyroidism. *Endocr Pract*. (2010) 16(6):977–81. doi: 10.4158/EP10052
12. Beierwaltes WH. Endocrine imaging: parathyroid, adrenal cortex and medulla, and other endocrine tumors. Part II. *J Nucl Med*. (1991) 32(8):1627–39.
13. Castellani M, Reschini E, Longari V, Paracchi A, Corbetta S, Marotta G, et al. Role of Tc-99 m sestamibi scintigraphy in the diagnosis and surgical decision-making process in primary hyperparathyroid disease. *Clin Nucl Med*. (2001) 26(2):139–44. doi: 10.1097/00003072-200102000-00010
14. McHenry CR. What's new in general surgery: endocrine surgery. *J Am Coll Surg*. (2002) 195(3):364–71. doi: 10.1016/s1072-7515(02)01307-8
15. Johnston LB, Carroll MJ, Britton KE, Lowe DG, Shand W, Besser GM, et al. The accuracy of parathyroid gland localization in primary hyperparathyroidism using sestamibi radionuclide imaging. *J Clin Endocrinol Metab*. (1996) 81(1):346–52. doi: 10.1210/jcem.81.1.8550776
16. Friedman K, Somervell H, Patel P, Melton GB, Garrett-Mayer E, Dackiw AP, et al. Effect of calcium channel blockers on the sensitivity of preoperative 99mTc-MIBI SPECT for hyperparathyroidism. *Surgery*. (2004) 136(6):1199–204. doi: 10.1016/j.surg.2004.06.047
17. Phillips IJ, Kurzawinski TR, Honour JW. Potential pitfalls in intraoperative parathyroid hormone measurements during parathyroid surgery. *Ann Clin Biochem*. (2005) 42(Pt 6):453–8. doi: 10.1258/000456305774538283
18. Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, et al. The American association of endocrine surgeons guidelines for definitive management of primary hyperparathyroidism. *JAMA Surg*. (2016) 151(10):959–68. doi: 10.1001/jamasurg.2016.2310
19. Wang CA. Surgical management of primary hyperparathyroidism. *Curr Probl Surg*. (1985) 22(11):1–50. doi: 10.1016/0011-3840(85)90019-x
20. Yamashita H, Noguchi S, Moriyama T, Takamatsu Y, Sadanaga K, Uchino S, et al. Reelevation of parathyroid hormone level after parathyroidectomy in patients with primary hyperparathyroidism: importance of decreased renal parathyroid hormone sensitivity. *Surgery*. (2005) 137(4):419–25. doi: 10.1016/j.surg.2004.12.009
21. Mizrachi A, Gilat H, Bachar G, Feinmesser R, Shpitzer T. Elevated parathyroid hormone levels after parathyroidectomy for primary hyperparathyroidism. *Head Neck*. (2009) 31(11):1456–60. doi: 10.1002/hed.21119
22. Carneiro DM, Solorzano CC, Irvin 3rd. GL, Recurrent disease after limited parathyroidectomy for sporadic primary hyperparathyroidism. *J Am Coll Surg*. (2004) 199(6):849–53. doi: 10.1016/j.jamcollsurg.2004.08.013
23. Solorzano CC, Mendez W, Lew JI, Rodgers SE, Montano R, Carneiro-Pla DM, et al. Long-term outcome of patients with elevated parathyroid hormone levels after successful parathyroidectomy for sporadic primary hyperparathyroidism. *Arch Surg*. (2008) 143(7):659–63. doi: 10.1001/archsurg.143.7.659
24. Nordenstrom E, Westerdahl J, Isaksson A, Lindblom P, Bergenfelz A. Patients with elevated serum parathyroid hormone levels after parathyroidectomy: showing signs of decreased peripheral parathyroid hormone sensitivity. *World J Surg*. (2003) 27(2):212–5. doi: 10.1007/s00268-002-6600-5
25. Charlett SD, Aye M, Atkin SL, England RJ. Defining failure after parathyroidectomy for primary hyperparathyroidism: case series. *J Laryngol Otol*. (2011) 125(4):394–8. doi: 10.1017/S0022215110002562
26. Yen TW, Wilson SD, Krzywda EA, Sugg SL. The role of parathyroid hormone measurements after surgery for primary hyperparathyroidism. *Surgery*. (2006) 140(4):665–72. doi: 10.1016/j.surg.2006.07.006
27. Holick MF. Vitamin D deficiency. *N Engl J Med*. (2007) 357(3):266–81. doi: 10.1056/NEJMra070553


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Surgery

TYPE Case Report
PUBLISHED 02 September 2022
DOI 10.3389/fsurg.2022.953989



OPEN ACCESS

EDITED BY
Nuria Maria Novoa,
University of Salamanca Health Care Complex, Spain

REVIEWED BY
Maria Teresa Gomez Hernandez,
University of Salamanca, Spain
Mehmet Ali Bedirhan,
Yedikule Teaching Hospital, Turkey

*CORRESPONDENCE
Chuan Zhong
zchuanhappy@126.com

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 26 May 2022
ACCEPTED 26 July 2022
PUBLISHED 02 September 2022

CITATION
Zhong C, Zhou H, Rami-Porta R and Zhao Y (2022) Case report: Primary pleural squamous cell carcinoma in a 68-year-old male.
Front. Surg. 9:953989.
doi: 10.3389/fsurg.2022.953989



# Case report: Primary pleural squamous cell carcinoma in a 68-year-old male

Chuan Zhong[1]*, Haining Zhou[1], Ramón Rami-Porta[2] and Yunfei Zhao[3]

[1]Department of Thoracic Surgery, Suining Central Hospital, Suining, China, [2]Department of Thoracic Surgery, Hospital Universitari Mútua Terrassa, University of Barcelona, Terrassa, Spain, [3]Department of Pathology, Suining Central Hospital, Suining, China

**Introduction:** Primary pleural squamous cell carcinoma (PPSCC) is a sporadic disease that is rarely reported in the literature. Due to its low incidence, the pathogenesis of PPSCC is unknown.
**Case summary:** We report a case of a 68-year-old male with PPSCC and sizable pulmonary bullae. Two months after complete resection of both lesions, a total dose of 50 Gy radiotherapy was administered over the operative field. After more than a year of follow-up, the patient is in steady condition without any sign of recurrence.
**Conclusion:** Since PPSCC is rarely reported, our case proposed that complete surgical resection combined with radiotherapy may be a promising therapeutic approach.

KEYWORDS

primary pleural squamous cell carcinoma, surgical resection, radiotherapy, pulmonary bullae, a promising therapeutic approach

## Introduction

Among epithelial tumors derived from the pleura, the most common are mesothelial tumors such as malignant mesothelioma (1). However, there is a rarely reported epithelial tumor that originates from the pleura—primary pleural squamous cell carcinoma (PPSCC) (2). Very few case reports have reported the incidence of this disease, and its pathogenic mechanism is poorly understood (3, 4). Therefore, there is no standard treatment for PPSCC. Herein, we report on a patient with a PPSCC case accompanied by pulmonary bullae, who completely recovered after receiving complete resection and radiotherapy. Our report will provide a reference for the treatment of PPSCC combined with pulmonary bullae.

## Case presentation

A 68-year-old male complained of right-sided chest pain for 4 months with no other symptoms. He did not have history of echinococcosis, tumor, or tuberculosis. However, he had been smoking 20 cigaretes and drinking 100 g of alcohol daily for 40 years. Physical examination revealed no relevant findings. Routine blood and urine tests showed no anemia or proteinuria, respectively. Computed tomography (CT) revealed thickened

pleura on the right anterolateral aspect of the chest wall, a soft tissue mass adjacent to the chest wall surrounding part of the 3rd and 4th ribs, a big pulmonary bulla with a size of 4.4 cm × 5.1 cm, and normal mediastinal lymph nodes (Figures 1A–C). We recommended PET/CT to the patient, who declined due to financial reasons. No positive lesion was found after a series of examinations were performed, including cranial magnetic resonance imaging (MRI), contrast-enhanced neck and abdominal CT scans, bronchoscopy, and whole body radionuclide bone scintigraphy. Because all these examinations did not reveal any evidence of regional or distant spread, invasive staging of the mediastinum by mediastinoscopy or of the pleural space by video-thoracoscopy was not indicated. The initial diagnosis was localized mesothelioma with pulmonary bulla. The lesion was deemed completely resectable, and the patient underwent right thoracotomy through the third intercostal space. The intraoperative exploration revealed that the mass of the subcutaneous tissue had a size of 4 cm × 5 cm, accompanied by a pleural lesion with a size of 5 cm × 6 cm. The internal margin of the lesion was attached to the edge of a small part of the adjacent bulla, but the wall of most of the remaining bulla was intact. Intraoperative frozen biopsy of the mass reported a malignant tumor, compatible with squamous cell carcinoma. Therefore, the tumor and bullae were entirely removed. The resection included the chest wall, part of the third and fourth ribs, tissues of the intercostal space and pleura, and a wedge resection of the pulmonary bulla. Appropriate nickel–titanium memory alloy embracing device was fixed on the third and fourth rib stumps to avoid the local collapse of the chest wall. The postoperative histopathological examination confirmed that the tumor was a squamous cell carcinoma that had invaded the adjacent ribs. The wall of the pulmonary bulla showed chronic inflammation (Figures 2A–D). The immunohistochemistry staining showed positive results of P63 and P40 and negative results of TTF1, napsin A, WT1, D2-40, c-kit, and calretinin (Figures 2E,F). Because there were no signs of tumor in other organs, such as lung, mediastinum, head, neck, and abdomen, it was diagnosed as a primary pleural tumor (5). There were no postoperative complications. Two months after the surgery, the patient returned and received radiotherapy over the operative field, with a total dose of 50 Gy. After more than a year of follow-up, no sign of tumor recurrence was detected (Figures 1D–F). The patient was satisfied to our treatment.

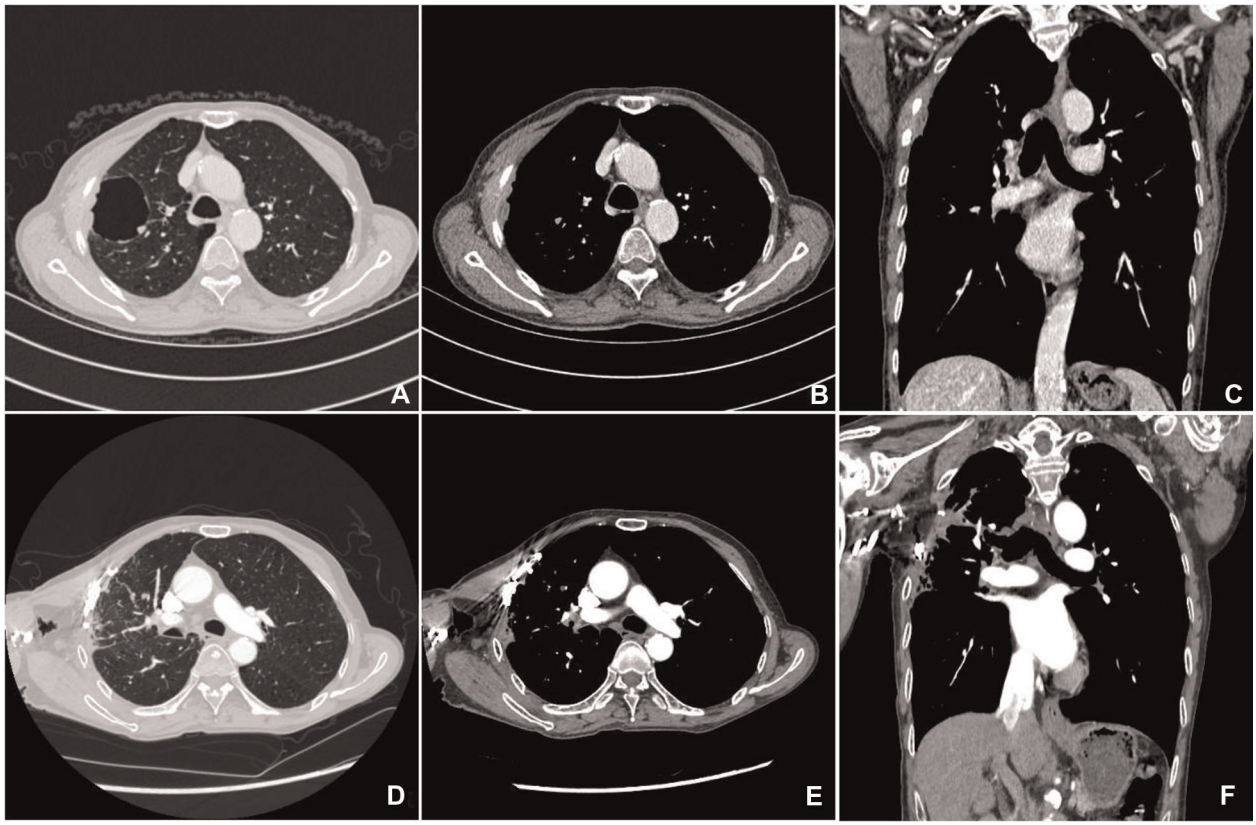


FIGURE 1
Preoperative chest CT scan (A–C); postoperative chest CT scan after more than a year of follow-up (D–F).

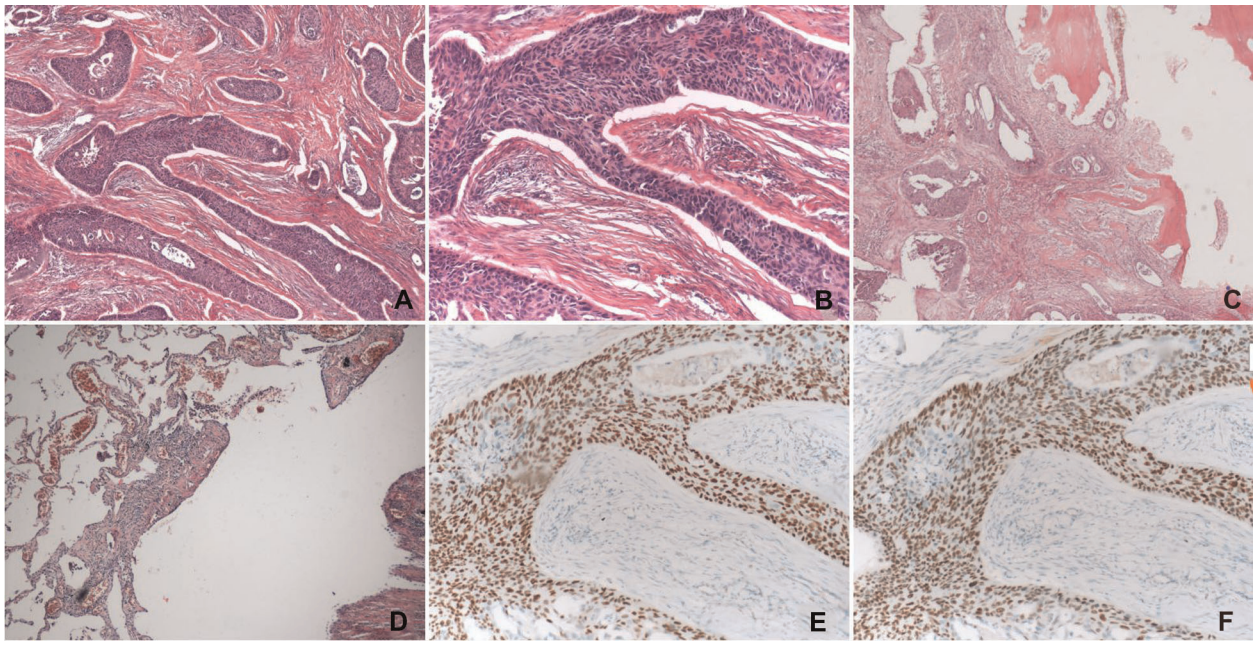


FIGURE 2
(A) The neoplastic cells were arranged in the form of nests with different sizes and showed various intercellular bridges (H&E stain, magnification ×40). (B) The cells were round or ovoid, with abundant cytoplasm, large nuclei, apparent nucleoli, and intracellular keratinization in focal areas (H&E stain, magnification ×100). (C) Squamous cell carcinoma invading the adjacent ribs (H&E stain, magnification ×40). (D) Pulmonary bullae with chronic inflammation (H&E stain, magnification ×40). (E,F) Immunohistochemical staining of neoplastic cells was performed with the use of antisera against p40 and p63, respectively, which showed evident nuclear positivity for both (E) p40 and (F) p63.

## Discussion

PPSCC is an extremely rare disease, with sporadic cases reported in the literature. Due to its low incidence, the pathogenesis of PPSCC remains largely unknown (4). Emerging evidence indicated that inflammation played a critical role in tumorigenesis (6). When tissues have chronic inflammation, the susceptibility to cancer will be promoted. In contrast, the long-term application of non-steroidal anti-inflammatory drugs will decrease the risk of several cancers (7). Previous studies suggested that chronic inflammation may be a pathogenic factor for PPSCC, which was supported by the fact that some patients with PPSCC had empyema, pleurocutaneous fistula (8), extrapleural pneumothorax without fistula in the treatment of tuberculosis (8), tuberculosis (9), or bronchopleural fistula caused by bronchiectasis (10). In this case, the presence of a pulmonary bulla with chronic inflammation in the vicinity of the tumor might promote neoplastic changes of the adjacent pleura, resulting in the development of squamous cell carcinoma. However, we are aware that this finding may be simply coincidental in our patient. Meanwhile, genetic deficiency may also account for the occurrence of PPSCC. Yoshida et al. reported that a 33-year-old female with extensive PPSCC had a deficiency of *SMARCB1/INI1* gene, which was a tumor suppressor gene. The loss of *SMARCB1* was associated with malignant tumors of the kidney, gastrointestinal tract, pancreas, and uterus (5). As for the diagnosis of PPSCC, there are no symptom which is specific for PPSCC. CT or PET–CT are typical approaches for the diagnosis of PPSCC. The preoperative biopsy using transthoracic Tru-Cut needle biopsy, is an approach for the diagnosis of pleural tumors. However, the diagnostic accuracy rate is not satisfactory (3). In this case, the differential diagnosis included focal mesothelioma, primary or secondary chest wall tumors, pleural metastasis, and thymic carcinoma, among which mesothelioma had the highest incidence rate. However, this potential was excluded by the diffuse expression of p40 and p63 and the negative expression of WT1, calretinin, and D2-40 in the tumor (4, 5, 11). Besides, primary chest wall tumors arise from muscle, fat, blood vessel, nerve sheath, cartilage, or bone of the chest wall. Therefore, the postoperative histopathological report of squamous cell carcinoma excluded the possibility of primary chest wall tumors. Furthermore, there was no tumor history and radiological evidence indicating that this tumor originated from lung, mediastinum, head, neck, or abdomen. Therefore, secondary chest wall tumors and pleural metastasis were further excluded. Although most thymic carcinomas were found to be squamous cell carcinoma, the tumor in the present case did not locate in the mediastinum and lacked the expression of CD117

(c-kit) that was a highly specific biomarker for thymic cancer (5). Consequently, we made the diagnosis of PPSCC.

Resection is a recommended approach for local tumors (4). Rüttner et al. reported that two PPSCC patients received surgery and were free of disease for 3 and 5 years after the operation, respectively (8). On the other hand, Prabhakar et al. reported that one PPSCC patient died from massive hemorrhage 5 months after resection. However, local or distant tumor recurrence could not be ruled out since necropsy was not performed (10). Sigala et al. reported that a patient with extensive PPSCC was treated with nivolumab after six cycles of cisplatinum and docetaxel combined with regional radiotherapy. Even though some tumor responses were observed, the tumor progressed locally and distantly, and the patient died 2 years after diagnosis (12). Besides, Yoshida et al. reported that a patient with extensive PPSCC died 10 months after diagnosis even treated with intensive chemotherapy (5). Therefore, chemotherapy might not be efficacious for PPSCC. In this case, the patient received complete resection and radiotherapy, and the follow-up indicated no tumor recurrence. Although no evidence suggested that radiotherapy could improve the prognosis of patients with PPSCC, our case report suggest that the combination of resection and adjuvant radiotherapy may be useful in the management of these patients.

## Conclusion

We reported a rare case of PPSCC combined with pulmonary bulla in an elderly patient. Complete surgical resection combined with radiotherapy achieved more than 1 year of disease-free survival, which may provide a reference for the treatment of PPSCC.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Suining Central Hospital. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

## Author contributions

Conceptualization: CZ; writing—original draft: CZ, HZ, and YZ; writing—review and editing: RR-P and CZ. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References

1. Galateau-Salle F, Churg A, Roggli V, Travis W.D, The World Health Organization committee for Tumors of the Pleura. The 2015 World Health Organization classification of tumors of the pleura: advances since the 2004 classification. *J Thorac Oncol*. (2016) 11(2):142–54. doi: 10.1016/j.jtho.2015.11.005

2. Franke M, Chung HD, Johnson FE. Squamous cell carcinoma arising from the pleura after pneumonectomy for squamous cell carcinoma of the lung. *Am J Surg*. (2010) 199:e34–5. doi: 10.1016/j.amjsurg.2009.05.004

3. Lin XM, Chi C, Chen J, Liu Y, Li P, Yang Y. Primary pleural squamous cell carcinoma misdiagnosed as localized mesothelioma: a case report and review of the literature. *J Cardiothorac Surg*. (2013) 8:50. doi: 10.1186/1749-8090-8-50

4. Ronchi A, Cozzolino I, Montella M, Vicidomini G, Morgillo F, Della Corte C M, et al. Primary pleural squamous cell carcinoma: a diagnostic challenge. *Cytopathology*. (2018) 29:205–7. doi: 10.1111/cyt.12498

5. Yoshida K, Fujiwara Y, Goto Y, Kohno T, Yoshida A, Tsuta K, et al. The first case of SMARCB1 (INI1)-deficient squamous cell carcinoma of the pleura: a case report. *BMC Cancer*. (2018) 18:398. doi: 10.1186/s12885-018-4321-x

6. Balkwill F, Coussens LM. Cancer: an inflammatory link. *Nature*. (2004) 431 (7007):405–6. doi: 10.1038/431405a

7. Gupta RA, Dubois RN. Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. *Nat Rev Cancer*. (2001) 1(1):11–21. doi: 10.1038/35094017

8. Rüttner JR, Heinzl S. Squamous-cell carcinoma of the pleura. *Thorax*. (1977) 32:497–500. doi: 10.1136/thx.32.4.497

9. Garty I, Straussberg R, Flatau E. Extraosseous 99mTc-MDP uptake in squamous cell carcinoma of the pleura. *Eur J Nucl Med*. (1987) 12:589–91. doi: 10.1007/BF00284531

10. Prabhakar G, Mitchell IM, Guha T, Norton R. Squamous cell carcinoma of the pleura following bronchopleural fistula. *Thorax*. (1989) 44:1053–4. doi: 10.1136/thx.44.12.1053

11. Ordóñez NG. Application of immunohistochemistry in the diagnosis of epithelioid mesothelioma: a review and update. *Hum Pathol*. (2013) 44(1):1–19. doi: 10.1016/j.humpath.2012.05.014

12. Sigala I, Alevizopoulos N, Elefteriou K, Gianniou N, Kalomenidis I. Primary squamous cell carcinoma of the pleura treated with nivolumab. *Respirol Case Rep*. (2020) 8:e00516. doi: 10.1002/rcr2.516

# Advantages of publishing in Frontiers

**OPEN ACCESS**
Articles are free to read for greatest visibility and readership

**FAST PUBLICATION**
Around 90 days from submission to decision

**HIGH QUALITY PEER-REVIEW**
Rigorous, collaborative, and constructive peer-review

**TRANSPARENT PEER-REVIEW**
Editors and reviewers acknowledged by name on published articles

**Frontiers**
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

**Visit us:** www.frontiersin.org
**Contact us:** frontiersin.org/about/contact

**REPRODUCIBILITY OF RESEARCH**
Support open data and methods to enhance research reproducibility

**DIGITAL PUBLISHING**
Articles designed for optimal readership across devices

**FOLLOW US**
@frontiersin

**IMPACT METRICS**
Advanced article metrics track visibility across digital media

**EXTENSIVE PROMOTION**
Marketing and promotion of impactful research

**LOOP RESEARCH NETWORK**
Our network increases your article's readership