

Early View

Invited review

ERS International Congress 2022: highlights from the Thoracic Surgery and Lung Transplantation Assembly

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Please cite this article as: Magouliotis DE, Bos S, Esendagli D, *et al.* ERS International Congress 2022: highlights from the Thoracic Surgery and Lung Transplantation Assembly. *ERJ Open Res* 2023; in press (<https://doi.org/10.1183/23120541.00671-2022>).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

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Title: ERS International Congress 2022: highlights from the Thoracic Surgery and Lung Transplantation Assembly

Running Head: ERS 2022 Assembly 8 Highlights

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Word count: 4,044

Abstract

The thoracic surgery and lung transplantation assembly (Assembly 8) of the European Respiratory Society (ERS) is delighted to present the highlights from the 2022 ERS International Congress that took place in a hybrid version in Barcelona, Spain. We have selected the four main sessions that discussed recent advances across a wide range of topics including the effects of COVID-19 on thoracic surgery and the challenges regarding lung transplantation in connective tissue diseases and common variable immunodeficiency (CVID). The sessions are summarized by early career members in close collaboration with the assembly faculty. We aim to provide the reader with an update and enhanced insight into the highlights of the conference in the fields of thoracic surgery and lung transplantation.

Keywords:

Thoracic Surgery

COVID-19

Lung transplantation

Connective tissue disease

Common variable immunodeficiency

Introduction

Assembly 8 includes physicians and surgeons with tremendous clinical expertise and a broad spectrum of research activities in state-of-the-art concepts regarding thoracic surgery (Group 8.1) and lung transplantation (Group 8.2). Group 8.1 includes surgeons with a special interest in an interdisciplinary approach toward various thoracic pathologies that may require surgical intervention as a part of the treatment strategy for either diagnostic/staging or therapeutic purposes. Furthermore, group 8.1 focuses on the possibilities of interactive sessions during the ERS International Congress to foster a culture of interdisciplinary collaboration between surgical and non-surgical members of the ERS. On the other hand, group 8.2 mainly consists of pulmonologists/respiratory and specialists/thoracic surgeons who have a special interest in lung transplantation. It is a group strongly engaged in working together to improve patient and donor selection and further enhance post-transplant morbidity, quality of life, and post-transplant survival outcomes. In the following paragraphs, we will explore the highlights and key concepts that were presented by members of Assembly 8 during this year's Annual Congress.

Group 8.1

The positive downside of COVID-19 pandemic on advances in thoracic surgery

Prof. René Petersen presented the important advances in thoracic surgery that occurred in 2022 despite the COVID-19 pandemic. The aims of his talk were the following: 1) to demonstrate the superiority of video-assisted thoracoscopic surgery (VATS) when performing lobectomy over the open approach, 2) the impact of implementing enhanced recovery after surgery (ERAS) strategies after performing VATS, 3) demonstrate the evidence for superiority of segmentectomy over lobectomy

in selected cases, and 4) highlight the future potential of combining immunotherapy with salvage surgery.

Prof. Petersen began his presentation with a recent study on VATS versus open lobectomy for early-stage lung cancer by Lim et al. [1]. This was a multicentre superiority Randomized Control Trial (RCT) that compared patients (1:1 VATS vs. open lobectomy) in early-stage lung cancer (T1-T3, N0-N1) [1]. The primary endpoint was physical functioning at five weeks using the EORTC QLQ-C30 questionnaire. The patients treated with VATS had superior physical functioning at five weeks after the procedure when compared to open lobectomy, but this difference was not seen at 12 months. Other endpoints like pain, length of stay, number of lymph nodes, and R0 resection did not differ between groups. Although the number of severe adverse events was similar between groups there were significantly fewer adverse events in the VATS-treated group. Consequently, VATS was associated with an enhanced physical function at five weeks after the procedure, but overall outcomes needs further follow-up to be fully unveiled.

The next topic discussed was the impact of enhanced recovery on clinical outcomes following VATS surgery. According to a single-center observational cohort study conducted by Huang et al., age and low lung function were significant risk factors for an extended length of in-hospital stay [2]. In addition, another study by the same team [3] highlighted the significant role of “days alive out of hospital” as a new metric of clinical outcomes following VATS in the context of an ERAS pathway. They also showed that air leaks, pneumonia, and recurrence represent the most common reasons for readmission and extended hospitalization following VATS [3].

A novel concept was the comparison between segmentectomy and lobectomy

for small-sized peripheral non-small cell lung cancer (NSCLC). In this context, Dr. Petersen presented the outcomes from the RCT JCOG0802, a multicentre, non-inferiority trial that incorporated patients from 70 Japanese institutions [4]. There was a median follow-up of 7.3 years, and segmentectomy was associated with a significantly higher median survival than lobectomy (94.3% vs. 91.1%, respectively; $p=0.0082$). Although the recurrence-free survival was similar between the two groups, the JCOG0802 Trial showed the incidence of local relapse to be significantly higher after segmentectomy (10.5%) than after lobectomy (5.4%) ($p=0.0018$).

Finally, Prof. Petersen presented data on the role of minimally invasive surgery following immuno-chemotherapy in 51 patients with initially unresectable stage III NSCLC [5]. Following immuno-chemotherapy, 31 patients (61%) were considered operable and all of them underwent VATS [5]. According to their findings, the addition of surgery after immuno-chemotherapy in initially unresectable cIIIB NSCLC is safe and is associated with significantly higher disease-free survival compared to those without (27.5 vs. 16.7 months).

Take-home messages

1. Patients undergoing VATS lobectomy had enhanced early physical function compared to thoracotomy, but similar surgical and oncological outcomes.
2. Segmentectomy was superior to lobectomy in terms of median survival for patients with small peripheral NSCLC, but with a significantly higher incidence of local recurrence.
3. Radical surgery following immuno-chemotherapy is associated with higher disease-free survival for patients with initially non-resectable cIIIB NSCLC.

Thoracic surgery and COVID-19 pandemic: an unexpected intimate relationship

In this session, experts debated the impact of COVID-19 on the field of thoracic surgery.

In the first part of her talk, Prof. Isabelle Opitz described the most common COVID-19-related complications that required surgical intervention, namely persistent pneumothorax, pneumatocele with persistent air leak, empyema, haemothorax, and acute respiratory distress syndrome (ARDS) that required extracorporeal membrane oxygenation (ECMO) and in some cases progressing into lung fibrosis with the occasional use of lung transplantation.

A monocentre observational study from the United States showed that 13 (0.7%) out of 1,954 patients admitted to hospital for COVID-19 (March-July 2020), required surgery, mostly due to pneumothorax and pneumatocele, with a survival rate of 77%. [6].

Another retrospective multicentre study including 83 patients with similar surgical complications (March-May 2021), had an overall 72% survival, with the most common cause of death being ARDS. Going into detail survival after surgical intervention for pneumothorax was reasonable (64%), surgical intervention of empyema had the best survival (76%), while haemothorax (46%) and hemoptysis (62%) had the worst prognosis. Multivariate analysis of morbidities related to postoperative complications showed an increased risk for older patients (HR 1.05, 95%CI: 1.01-1.10, $p=0.023$) [7].

In the second part of her talk, Prof. Opitz described the relationship between COVID-19 and thoracic malignancies. Data from the University Hospital of Zurich

between 2019 and 2020 showed that despite the ongoing pandemic prompt surgical treatment of patients with thoracic malignancies was guaranteed, without any increased incidence of advanced-stage thoracic malignancies. Moreover, among 50 patients hospitalised for thoracic surgery during the pandemic, only six experienced COVID-19 symptoms [8].

The TERA-VOLT analysis, a multicentre (28 institutions from Europe, North America, South America, Asia) collaborative study on 346 patients with chest malignancies (86% NSCLC) and COVID-19 reported different results. In this cohort a delayed cancer treatment was found in 57% of patients. Furthermore, patients with NSCLC showed an increased risk of contracting COVID-19 infection, with a worse course of the disease. This could be explained by the wide range of centres from many countries with different exposure to the pandemic. COVID-19 vaccination showed a protective effect on hospitalisation and death (OR = 0.30, 95%CI: 0.15-0.57, $p = 0.0003$) [9].

This was also seen in a nationwide analysis from Asia, which where a considerable number of cancer patients experienced complications due to COVID-19 infection (HR 3.56, 95%CI 1.65-7.69) [10].

Exploring the possible transmission of COVID-19 to healthcare providers while performing minimally invasive surgery, through the CO₂ or the plume created by electrocautery was not shown. [11].

Prof. Marco Lucchi discussed tracheal complications related to COVID-19. He reported a cohort of 98 patients with COVID-19 who developed severe respiratory failure, and of whom 30 underwent prolonged invasive ventilation (≥ 14 days). Severe tracheal complications occurred in 47% of cases: full-thickness tracheal lesions

(10/30, 33%) or tracheoesophageal fistulas (4/30, 13%), The clinical manifestations were subcutaneous emphysema (43%), pneumomediastinum (33%) and pneumothorax (20%) with a high mortality rate (27%). Factors that might be related to the incidence of tracheal complications are pronation maneuvers (increasing the cuff pressure on the tracheal wall), high doses of systemic steroids, microvascular injury related to COVID-19, and high viral replication of the virus within the tracheal epithelium [12].

Prof. Lucchi further reported a single-centre experience from the University Hospital of Pisa, regarding tracheal laceration related to intubation or tracheotomy. Out of ten tracheal lacerations, eight patients were treated conservatively, while two cases required surgical intervention, according to their previously reported technique [13]. Four cases with tracheoesophageal fistula were treated either conservatively or with the standard Grillo's technique, where the oesophageal wall is sutured directly and the sternocleidomastoid muscle interposed between the oesophagus and trachea, followed by tracheal resection and reconstruction. The two patients who were treated conservatively, unfortunately, died while the two who underwent surgery were successfully discharged.

Lastly, one of the most important late complications of tracheotomy or prolonged intubation is tracheal stenosis [14]. Prof. Lucchi presented a case of laryngotracheal resection after post-tracheotomy stenosis in a patient with COVID-19, showing that both macroscopically and microscopically, the mucosa and tracheal tissues were characterised by inflammatory infiltrate and necrosis that may delay healing of the anastomosis [15].

Take-home messages

1. Pneumothorax, pneumatocele, empyema, and haemothorax were the most common indications for thoracic surgical interventions in patients with COVID-19.
2. Patients with thoracic malignancies were at increased risk of a severe course of COVID-19 disease.
3. Tracheal complications is a common complication in mechanically ventilated COVID-19 patients, that require a tailored approach.

Group 8.2

Lung involvement in common variable immunodeficiency (CVID): from diagnosis to lung transplantation

Dr. Pere Soler discussed the pathogenesis and diagnosis of CVID in both paediatric and adult patients. CVID is characterised by genetic, immunological and clinical heterogeneity, which makes the process of reaching this diagnosis challenging. Currently over 40 genetic defects have been identified in patients with a CVID phenotype, which is not considered CVID. Excluding other primary antibody deficiencies or secondary causes of hypogammaglobulinaemia is important when establishing the CVID diagnosis [16-19]. The common immune defect in CVID patients is, based on the loss of B-cell function, a relative loss of T-cells function and defects in thymus maturation, monocyte/dendritic cell defects, and impaired innate immune responses including loss of natural killer cells [16-19]. For the diagnosis, it is important to use age-adapted reference values for immunoglobulins, T and B cell subsets and also to perform a differential diagnosis of hypogammaglobulinaemia [20,21]. CVID patients present with recurrent upper and lower respiratory tract

infections, bronchiectasis, lung function decline, gastrointestinal infections, autoimmune enteropathy, and lymphadenopathies, thus requiring a multidisciplinary approach. Pere Soler emphasized the importance of genetics in CVID and recommended testing all patients, and especially those with early age onset of disease (younger than 5 years of age), those with infection-plus phenotype (presence of infection), and those with increased number of transitional B cells.

Dr. David M. Lowe pointed out that the respiratory tract (both upper and lower) is abnormal in CVID patients. Sputum analysis of these patients showed an increase in pro-inflammatory cytokines like IL-1, IL-6, IL-8, TNF- α , IL-5, IL-13, even in patients with radiologically normal airways, thus suggesting the presence of chronic inflammation. In contrast to normal, patients with CVID do not excrete IgA in their airways but do have increased IgG as a consequence of treatment with immunoglobulin replacement, which is considered standard. Nonetheless, this is insufficient to completely prevent pulmonary inflammation and infections [22]. Moreover, CVID patients have an altered microbiome. The more diverse the microbiome, the more inflammation and airway damage occurs [22]. Another problem with the recurrent usage of antibiotics for this group of patients, including macrolide prophylaxis, is the increased incidence of antimicrobial resistance.

Antibiotic use is frequent in this group: on average 0.36 courses of antibiotics per patient/month [23]. Because viruses are especially dominant in acute respiratory infections, antibiotics are often not required, and should be selected for established bacterial infection, where treatment should be extended and be given for two weeks.

Antibiotic prophylaxis to prevent infections has been shown to delay the time to antibiotic usage and reduce hospitalization, but had no effect on forced expiratory

volume in one second [24]. Other measures to prevent infections, apart from intravenous immunoglobulin (IVIG) treatment and antibiotic prophylaxis, are advice on nutritional intake, occupation, travel, smoking, sputum clearance, physiotherapy and vaccines for patients and their household members.

Additional challenges that can be encountered in patients with CVID are colonization with *Haemophilus influenza* or *Pseudomonas aeruginosa*, chronic sinusitis, mycobacterial infections, and atypical extrapulmonary infections. Presentations may be atypical, and diagnosis and treatment are challenging.

Dr. Elisabetta Renzoni discussed the non-infectious lung involvement in CVID patients with a focus on CVID-associated Interstitial Lung Disease (Granulomatous Lymphocytic-ILD; GLILD), which is a lung manifestation of systemic immune dysregulation. According to BLF/UK consensus statement, GLILD is a distinct clinic-radiopathological interstitial lung disease (ILD) occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granulomata in the lung, and in whom other conditions have been considered and excluded [25]. GLILD occurs in approximately 10-30% of CVID patients and consists of a multi-system immune dysregulation often associated with splenomegaly, adenopathy, autoimmune diseases, and gastrointestinal/hepatic disease [26,27]. GLILD can be misdiagnosed as sarcoidosis and patients should be tested for serum (pan) hypogammaglobulinaemia and lack of antibody production following immunization (especially used in patients with sarcoidosis) [28]. Recurrent infections, autoimmune disease, splenomegaly, hepatomegaly and diffuse adenopathies are findings that are more common in GLILD (13). There is a wide range of histopathological findings that often include a combination of granulomatous and lymphocytic infiltrates and a

variety of patterns like follicular bronchiolitis, lymphocytic interstitial pneumonia, diffuse or nodular lymphoid hyperplasia together with areas of organising pneumonia [29]. Management of the disease according to the BLF/UK consensus includes IVIG and GLILD-specific treatment in case of deteriorating lung function. This consists of corticosteroids as the first-line treatment and azathioprine, rituximab or mycophenolate as a second-line therapy [25]. The treatment should be individualized according to comorbidities and patient preferences. Yet management is highly complex due to limited experience and further studies are needed.

Lastly, Dr. Michael Perch pointed out that the primary goal of lung transplantation is to provide a survival benefit. The mean survival of lung transplant patients, even though it has improved over years, is still on average 7 years [30]. According to the latest version of the consensus document for the selection of lung transplant candidates, patients are classified according to risk factors [31]. Candidates with conditions classified as absolute contraindications are at too high a risk for achieving a successful outcome post lung transplantation and should not undergo transplantation except in very exceptional circumstances [31]. Candidates who have risk factors with high or substantially increased risk should only be considered in centres with expertise for these specific conditions as these risk factors are associated with unfavourable short- and/or long-term outcomes. Some of these risk factors are high age and body mass index, heart or kidney disease, difficult to treat chronic infections etc. [31]. The presence of more than one risk factors is thought to be multiplicative in terms of increasing the risk of adverse outcomes post-transplant [31].

Lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all these criteria: 1. High risk of death from lung disease

within two years if transplantation is not performed. 2. High likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function [31]. Listing for transplantation should occur when life expectancy is greatly reduced but nonetheless greater than the expected waiting time. Modifiable conditions should be optimized if possible.

Regarding lung transplantation for end-stage lung disease in CVID there is a limited experience, mostly obtained from cases. In several cases it was found that patients can mount sufficient T-cell responses to cause acute cellular rejection and at the same time had signs of both infection and inflammation, resulting in early mortality and limited survival benefit.

Nathan JA et al. reported a median survival of 4 years after lung transplantation for bronchiectasis related to immunodeficiency, despite receiving IVIG after transplantation [34]. In this series, survival was similar to patients transplanted for other indications, but overall this survival was rather limited and not in line with current aims after transplantation.

Taking in consideration the present data CVID is not simply the absence of IgG. Lung transplantation for CVID is highly complicated and needs a multidisciplinary approach in an experienced transplant centre. After transplantation, continuation of IVIG treatment and antimicrobial prophylaxis should be tailored carefully and further studies regarding complications and outcome are needed regarding this complex group of patients.

Take-home messages

1. CVID is characterised by genetic, immunological, and clinical heterogeneity. Common features of CVID are: 1) immunological (eg. loss of B-cell function, a relative loss of T-cells function and NK cells, defects in thymus maturation, and monocyte/dendritic cell defects); 2) clinical (eg. recurrent upper and lower respiratory tract infections, bronchiectasis, lung function decline, gastrointestinal infections, autoimmune enteropathy, and lymphadenopathies); 3) genetic, thus making genetic testing recommended especially in those patients with early age onset of the disease.
2. CVID patients have chronic inflammation and altered microbiome in the lungs and frequent usage of antibiotics can lead to resistance, thus multiple measures to prevent infections should be taken.
3. CVID is associated with systemic immune dysregulation that may lead to GLILD,
4. Lung transplantation for CVID is highly complex given the potential co-occurrence of acute rejection and infection episodes, and long-term outcomes are uncertain.

Interstitial lung diseases in connective tissue diseases: patient's journey from diagnosis and new treatment strategies to transplantation

Prof. Antoine Froidure started the session on ILD in connective tissue diseases (CTD) and highlighted that genetic testing has changed the way we practise medicine in recent years. From a physician's perspective, it can help understand underlying disease mechanisms, refine diagnosis, identify patients at risk, genetic counselling and

prevention, and may have therapeutic implications.¹ There are also advantages from a patient's perspective, such as the ability to understand their own disease and to know whether relatives are at risk. On the other hand, genetic testing can also negatively affect the patient with fear, stress, uncertainty and socio-economic consequences [35].

With regard to ILD, we know that the risk of CTD-ILD is higher in patients with systemic sclerosis and inflammatory myositis compared to rheumatoid arthritis (RA) and Sjögren's syndrome [36]. It was recently detected that variants of the MUC5B promotor are not only related to idiopathic pulmonary fibrosis, but also make patients with RA more prone to develop lung fibrosis [37,38]. Along with other risk factors such as male and age, the risk to develop subclinical RA-ILD can be as high as 94.5% [37,38]. However, the presence of a MUC5B variant is not a predictor for disease progression [38].

Finally, Prof. Antoine Froidure emphasised the importance of telomere-related gene mutations, which are not only correlated with a risk of idiopathic pulmonary fibrosis, but also lung fibrosis in CTD [39].

Secondly, Prof. Bruno Crestani focused on the diagnosis of CTD-ILD and new treatment strategies. CTD-ILD accounts for an important part of ILD and multidisciplinary discussion is essential because of heterogeneity of phenotypes [40]. High-resolution computed tomography remains the gold standard for diagnosis and is also the best screening tool, although other tools such as lung ultrasound, electronic stethoscope, exhaled air, blood biomarkers and risk scores are being investigated [41].

Treatment of CTD-ILD is evolving rapidly and ranges from corticosteroids and immunomodulators (e.g., rituximab [42,43], cyclophosphamide, mycophenolate mofetil, tocilizumab [44,45]) to antifibrotic agents (nintedanib [46-48], pirfenidone [49,50]) based on the degree of inflammation and fibrosis. Interestingly, methotrexate

may delay the onset of ILD in patients with RA [51], while withdrawal can accelerate disease progression [52]. As such, methotrexate might become the treatment of choice in RA-ILD and should not be discontinued upon ILD detection unless there is clear suspicion of methotrexate-associated ILD, although rare [53]. To determine the best therapeutic strategies, disease-specific algorithms should be pursued and an ERS/EULAR clinical practice guideline for CTD-ILD screening, diagnosis and treatment is underway.

Lung transplantation is a reasonable treatment option for carefully selected end-stage CTD-ILD patients and Prof. José Cifrián addressed the main challenges if a CTD-ILD patient is referred for lung transplantation. An updated consensus document on the selection of lung transplant candidates from the International Society for Heart and Lung Transplantation has recently become available [54], as is a consensus document on the evaluation of CTD candidates [55]. The latter aims to standardise the evaluation, listing and post-transplant management of CTD candidates to allow for risk stratification, as these patients often have specific risk factors that may increase the risk of unfavourable short- and long-term post-transplant outcomes [55]. On the other hand, outcomes comparable to patients with other types of ILD were observed in well-selected patients with systemic sclerosis and RA, and outcomes for systemic lupus erythematosus and polymyositis and dermatomyositis were comparable to idiopathic pulmonary fibrosis [55].

When considering a CTD-ILD patient for lung transplantation, thorough evaluation of extrapulmonary manifestations of CTD is critical. Involvement of a multidisciplinary team in pre-transplant evaluation and selection and post-transplant care is essential to optimise outcomes [56]. Detailed organ-specific evaluation recommendations can be found in the consensus document and the ones highlighted

by Prof. J. Cifrián are summarised in table 1 [55]. Absolute contraindications for lung transplantation are mainly related to persistent, active extrapulmonary manifestations despite maximal therapy [55].

Because of the medical complexity of CTD-patients, early referral (“the sooner the better”) to a lung transplant centre is recommended, also to identify modifiable risk factors that could improve the candidacy for lung transplantation or survival [55].

Lastly, Prof. Ingrid Lundberg concluded the session by discussing new trends in the treatment of myositis-associated ILD. An increasing number of autoantibodies specific for myositis have been detected that are not found in other auto-immune diseases [57]. These 16 myositis-specific antibodies are associated with specific clinical phenotypes [57], some of which have a strong association with lung disease (i.e., anti-MDA5 [58] and anti-synthetase antibodies [59]). Detection of antibodies can guide the diagnosis as patients may present with symptoms varying from myositis, ILD, concomitant myositis and ILD to polyarthritis without ILD or myositis [60]. Patients with anti-MDA5 antibodies are especially at risk for rapidly progressive ILD [58].

Currently, no randomised controlled trials regarding optimal treatment are available. Expert recommendations divide treatment of myositis-associated ILD into two groups based on disease severity (mild-moderate and severe) and treatment options are relatively similar to those for other CTD-ILD, including corticosteroids, cyclophosphamide, rituximab, mycophenolate mofetil, calcineurin inhibitors but also JAK inhibitors. For progressive disease, abatacept is being tested in clinical trials [61].

Finally, as mentioned in all CTD-ILD presentations, I. Lundberg ended by emphasising the importance of multidisciplinary management because of the complexity of cases.

Take-home messages

1. Genetic testing enhances pathobiology research, diagnostic and risk-stratification work-up, genetic counselling, along with prevention and treatment.
2. Treatment of CTD-ILD ranges from corticosteroids and immunomodulators to antifibrotic agents based on the degree of inflammation and fibrosis. Lung transplantation is a reasonable treatment option for carefully selected end-stage CTD-ILD patients
3. A multidisciplinary approach in the diagnosis and management of CTD-ILD and in the selection and care of lung transplant candidates is essential because of the heterogeneity and complexity.
4. Thorough assessment and treatment of extrapulmonary manifestations of CTD is critical in the evaluation and selection of lung transplant candidates to optimise outcomes as well as early referral.

Conclusion

Owing to the ongoing COVID-19 pandemic, this year's congress was in a hybrid form. Once again the Annual ERS Congress was a great success. Topics were very diverse and included important sessions on innovation and state-of-the-art in thoracic surgery and lung transplantation. In this article, we have summarised the highlights of the most important sessions in the field of thoracic surgery and lung transplantations

of this year's congress, representing a wide range of topics. We look forward to the next ERS International Congress, to be held in Milan, Italy, from 9 to 13 September 2023.

Conflicts of Interest

The participating authors declare no conflicts of interest.

Ethical Approval

Does not apply.

Informed Consent

Does not apply.

Acknowledgements

Does not apply.

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Table 1: Organ-specific risks and considerations in CTD-ILD candidates based on the ISHLT consensus document²¹ and highlighted by J. Cifrián

Gastrointestinal	<ul style="list-style-type: none"> - In SSc, ineffective or absent oesophageal peristalsis leading to reflux occurs in 75-80% of patients, gastroparesis in up to 50% and small intestinal bacterial overgrowth in 30-60% of patients. - A 24h pH-metry with impedance testing and manometry is recommended. - Computed tomography can reveal oesophageal dysfunction by dilatation and/or air-fluid levels. - Input from a nutritionist is important pre- and post-transplant. - Patients with severe gastroesophageal reflux or oesophageal dysfunction should be evaluated for anti-reflux surgery.
Cardiac	<ul style="list-style-type: none"> - Myocarditis, pericarditis, congestive heart failure or conduction defects are seen in 7-39% of SSc and 50% of SLE patients. Myocarditis is also possible in PM/DM. - The incidence of myocardial infarction is five times higher in SLE than in the general population due to premature atherosclerosis. - Cardiac MRI is recommended in cases of suspected myocarditis, abnormal rhythm on Holter monitoring or restrictive cardiomyopathy on echocardiogram. - To confirm active inflammation, a myocardial biopsy is needed.
Haematological	<ul style="list-style-type: none"> - Cytopenia is detected in 30-60% of patients with Sjögren. - In progressive SSc, 20-50% has hypergammaglobulinemia and 10-15% MGUS. - There is an increased risk of venous thromboembolism if

	<p>antiphospholipid antibodies are present (10-43% in SSc, 35% in SLE).</p> <ul style="list-style-type: none"> - A hypercoagulable evaluation for the risk of thrombophilia is recommended, as is a haematological evaluation for patients with antiphospholipid antibodies. - In patients treated with rituximab or mycophenolate mofetil, immunoglobulin levels should be checked.
Oncological	<ul style="list-style-type: none"> - Patients with Sjögren have a 15-20-fold risk of malignant lymphoid disorders. - B-cell lymphomas are seen in 5% of progressive SSc patients. - Patients should be screened for risk factors for B-cell lymphomas and a PET-scan should be performed if ESSDAI index ≥ 5 with 3 or more risk factors. - Special attention should be paid to patients with PM/DM because of the risk of cancer-associated myositis.
Renal	<ul style="list-style-type: none"> - Scleroderma renal crisis occurs in 5-85% of SSc patients. Risk factors include rapid progression of skin fibrosis, diffuse cutaneous scleroderma, disease duration of less than 4 years, presence of anti-RNA polymerase III antibodies and high-dose steroids (prednisolone > 15 mg/day). - Up to 50% of SLE patients develop lupus nephritis.
Vascular	<ul style="list-style-type: none"> - Risk of digital ischaemia due to Raynaud's phenomenon in 95% of SSc patients, with digital ulcers in 30-50% and risk of amputation in 20%. - Rheumatological evaluation is important to assess the severity of Raynaud's phenomenon, along with an arterial doppler of upper and

	lower extremities.
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CTD-ILD: connective tissue disease-related interstitial lung disease, ESSDAI: EULAR Sjögren's syndrome disease activity index, ISHLT: International Society for Heart and Lung Transplantation, MGUS: monoclonal gammopathy of undetermined significance, PET: positron emission tomography, PM/DM: polymyositis and dermatomyositis, SLE: systemic lupus erythematosus, SSc: systemic sclerosis.