



The impact of COVID-19 pandemic on pulmonary hypertension: What have we learned?

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Abstract

The coronavirus 2019 disease (COVID-19) pandemic threatened the Spanish health-care system. Patients with demanding conditions such as precapillary pulmonary hypertension (PH) faced a potentially severe infection, while their usual access to medical care was restricted. This prospective, unicentric study assessed the impact of COVID-19 on PH patients' outcomes and the operational changes in the PH network. Sixty-three PH patients (41 pulmonary arterial hypertension [PAH]; 22 chronic thromboembolic pulmonary hypertension [CTEPH]) experienced COVID-19. Overall mortality was 9.5% without differences when stratifying by hemodynamics or PAH-risk score. Patients who died were older (73.6 ± 5 vs. 52.2 ± 15.4 ; $p = 0.001$), with more comorbidities (higher Charlson index: 4.17 ± 2.48 vs. 1.14 ± 1.67 ; $p = 0.0002$). Referrals to the PH expert center decreased compared to the previous 3 years (123 vs. 160; $p = 0.002$). The outpatient activity shifted toward greater use of telemedicine. Balloon pulmonary angioplasty activity could be maintained after the first pandemic wave and lockdown while pulmonary thromboendarterectomy procedures decreased (19 vs. 36; $p = 0.017$). Pulmonary transplantation activity remained similar. The COVID-19 mortality in PAH/CTEPH patients was not related to hemodynamic severity or risk stratification, but to comorbidities. The pandemic imposed structural changes but a planned organization and resource reallocation made it possible to maintain PH patients' care.

Abbreviations: BPA, balloon pulmonary angioplasty; COVID-19, coronavirus 2019 disease; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary artery hypertension; PH, pulmonary hypertension; PTE, pulmonary thromboendarterectomy.

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KEYWORDS

chronic thromboembolic pulmonary hypertension, COVID-19 infection, pulmonary arterial hypertension, telemedicine

INTRODUCTION

The coronavirus 2019 disease (COVID-19) has led to high mortality, particularly in patients with comorbidities.¹ Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are rare chronic diseases with a high risk of mortality during hospitalizations for noncardiovascular conditions.² However, data are scarce regarding the COVID-19 incidence and outcomes in patients with pulmonary vascular disease.

After the outbreak, many healthcare professionals were diverted from their usual activity, and resources were rechanneled for COVID-19 care. Moreover, many people tried to avoid any healthcare contact because of the fear of infection. This translated into a reduced utilization of health assistance, a decrease in inter-hospital referrals, a shift from face-to-face activity in the outpatient clinic to a teleconsultation model, and to reduced hospitalizations of patients with non-COVID-19.^{3,4}

The correct management of pulmonary hypertension (PH) requires highly specialized care, concentrated in a small number of referral units. Under standard conditions, the most severe patients or those requiring complex treatments are referred to PH expert centers where pulmonary thromboendarterectomy (PTE), balloon pulmonary angioplasty (BPA), and lung transplantation are performed. It has been challenging for the health system to provide the required attention to the COVID-19 pandemic while maintaining the appropriate clinical follow-up and treatments for PH patients.

We analyzed the clinical characteristics and outcomes of PAH and CTEPH patients with COVID-19 in a reference center. We also evaluated the changes implemented in our PH network and the impact of COVID-19 on the treatments offered to PH patients without COVID-19.

METHODS**Study population**

This is a single-center prospective study of consecutive cases previously diagnosed with PAH and CTEPH according to the ESC/ERS criteria⁵ with confirmed

COVID-19 between March 2020 and March 2021. COVID-19 diagnosis was made either by a polymerase chain reaction testing positive result and/or the presence of clinical or radiological diagnostic features.⁶ All the patients were in active follow-up in pulmonary hypertension national expert center, which attends to 30% of patients with PAH and CTEPH in Spain. We excluded three patients who were responders to calcium channel blockers with normal pulmonary pressures. Data were collected from medical reports. All patients were included in REHAP (Registro Español de Hipertensión Pulmonar) after signing an informed consent form. We analyzed the baseline characteristics, hemodynamics, disease severity, medical treatment, and comorbidities in survivors and nonsurvivors after COVID-19 infection.

The risk stratification was performed following the noninvasive French model that uses three criteria: functional class, NT-ProBNP, and 6-min walking distance. Low risk was considered when the three low-risk criteria were present, and high risk when there was none.⁷ These data were collected from the last consultation before COVID-19 infection. We analyzed the impact of comorbidities on prognosis according to the presence or absence of at least one risk factor for left heart disease: diabetes mellitus, evidence of significant coronary artery disease, history of essential hypertension or body mass index $> 30 \text{ kg/m}^2$, as it was proposed in the cluster analysis from the Compera registry⁸; whereas the overall comorbidity was analyzed according to the Charlson index.⁹

We evaluated the specific treatment used in patients with PAH and COVID according to the hospital treatment protocol in each pandemic wave. Antipyretics, analgesics, and mucolytics were considered symptomatic treatments.

The monthly consultation structure over the first 12 months of the COVID-19 pandemic (March 2020–February 2021) was compared to the previous year (March 2019–February 2020). Two care-models were considered for analysis: telemedicine (structured telephone call) and face-to-face consultation.

We studied the referral rates of adult patients with confirmed CTEPH or PAH, the number of PTE, BPA, and lung transplants over the first 12 months of the COVID-19 pandemic (March 2020–February 2021) and compared them with the previous 3 years.

Statistical analysis

Categorical variables are reported as absolute and relative frequencies, and compared with Pearson's or Fisher's exact tests, as appropriate. Continuous variables are reported as means (standard deviation) or medians (interquartile range) and compared with *t*-tests or Mann–Whitney *U*-tests, as appropriate. The data analysis uses Stata version 14.0 (StataCorp) and R studio v 4.0.3.

RESULTS

Patients diagnosed with PAH/CTEPH and intercurrent COVID-19 infection

The incidence of COVID-19 infection was 8% (63 cases of 800 patients in active follow-up at our center). The mean age of those patients was 53.6 ± 15.9 years, and 64% were women. PAH was the most frequent group (66.6%), of which 63% were at low risk despite the hemodynamic severity (mean pulmonary artery pressure 42.9 ± 13.8 mmHg, pulmonary vascular resistance 7.4 ± 5.2 Wood units, and cardiac index 2.8 ± 0.7 L/min/m²). Almost all patients received vasodilator drugs (96.8%). Of them, 36.1% were on monotherapy, 39.3% on combination therapy, and 24.6% on triple therapy.

The incidence rate remained the same in every pandemic wave. A positive COVID-19 test was present in 89.4% of the cases, while the remaining were clinically diagnosed, all during the first wave.

The infection took an asymptomatic course in five cases (8%), it was mildly symptomatic in 37 (58.7%) and presented with pneumonia in 24 patients (38.1%). Twenty-eight patients (44.4%) required hospitalization. The specific treatment varied according to the pandemic wave. Hydroxychloroquine and azithromycin were used in 29% of the cases, mainly during the first and second pandemic wave, whereas corticosteroid treatment was prescribed in 45% of patients and tocilizumab in 20.8%.

Overall mortality was 9.5% (six patients), whereas the in-hospital mortality was 21.4%. No death occurred in outpatients. The patients who died were older, with a higher Charlson index and higher prevalence of ≥ 1 risk factors for left heart disease compared to the survivor group. Differences in mortality according to sex, PH subtype, risk stratification score, vasodilator treatment, or hemodynamic values were not observed (Table 1). The deceased group was most frequently treated with antibiotics ($p = 0.027$), tocilizumab ($p = 0.037$), corticosteroid ($p = 0.027$), and oxygen ($p = 0.005$).

Patients diagnosed with PAH/CTEPH without COVID-19 infection

Patients' assessment

There was a significant decrease in referrals to the PH expert center for PAH and CTEPH new patients compared to the mean of the previous 3 years (a mean of 159 referrals per year during the previous 3 years vs. 123 during 2020; $p = 0.006$). Teleconsultation was the most frequent way of patient contact since the pandemic outbreak, representing 57.1% of the outpatient activity, while in the same period of the previous year it was 14.3% ($p < 0.001$). The first consultation was conducted over the phone in 19.6% of the cases, while all of them had been face-to-face in the previous year. The incorporation of telemedicine enabled follow-ups and even increased the number of patients attended (8.71 vs. 7.04 patients/day) during the studied period (Figure 1).

An average of 35 daily email consultations were received. Most of them (75%) could be resolved via email. A phone consultation was required in 20% of the cases, while 5% of the patients who consulted via email were advised to seek face-to-face medical assistance.

There was a 46% decrease in the initiation of new PH-specific drugs compared to the mean of the 3 previous years. PH specialist nurses performed the follow-ups to monitor medication side effects.

PTE, BPA, and lung transplantation

There was a significant decrease in the number of BPA carried out during 2020 compared to the previous 3 years (70 procedures in 2020 vs. a mean of 97; $p = 0.015$). However, excluding the lockdown period (3 months, from March to May 2020), there were no differences compared to the same period of the previous year (67 vs. 72; $p = 0.623$). Regarding the number of PTE, there was a significant decrease in the number of procedures during 2020 compared with the mean of procedures carried out during the previous 3 years (19 procedures in 2020 vs. a mean of 36 surgeries in the 2017–2019 era; $p = 0.017$) (Figure 2).

There were seven PH patients who underwent bilateral lung transplantation because of advanced pulmonary arterial hypertension, six electively and one urgently, compared to four procedures during the same period of the previous year. Survival was similar to the previous year.

	Survivors (n = 57)	Nonsurvivors (n = 6)	p < 0.005
Woman (%)	44 (71.9)	2 (33.3)	0.053
Age (years)	52.2 ± 15.4	73.6 ± 5.0	0.001
Etiology (%)			
CTEPH	19 (33.3)	3 (50.0)	0.415
PAH	38 (66.7)	3 (50.0)	
Charlson index (number)	1.14 ± 1.67	4.17 ± 2.48	0.0002
≥1 Risk Factors LHD	41.7%	83.3%	0.052
ESC risk score (%)			
Low risk	36 (63.2)	3 (50.0)	0.627
Medium risk	13 (22.8)	2 (33.3)	
High risk	7 (12.3)	1 (16.7)	
Treatment (%)			
Vasodilator monotherapy	20 (35.1)	2 (33.3)	0.233
Dual vasodilator therapy	20 (35.1)	4 (66.7)	
Triple vasodilator therapy	15 (26.3)	0	
Previous anticoagulant therapy (%)	29 (50.9)	3 (50)	0.967
Previous oxygen therapy (%)	16 (28.1)	3 (50.0)	0.266
Hemodynamic			
mPAP (mmHg)	42.8 ± 14.1	44.3 ± 12.4	0.804
PVR (Wood Unit)	7.4 ± 5.3	8.3 ± 5.1	0.670
CI (L/min/m ²)	2.9 ± 0.8	2.4 ± 0.4	0.137
Number of COVID therapy	1.7 ± 1.7	3.7 ± 1.2	0.009
Symptomatic treatment ^a (%)	32 (56.1)	1 (16.7)	0.066
Mild symptoms (%)	35 (61.4)	0 (0.0)	0.004
Hospitalization (%)	17 (29.8)	6 (100)	0.001
Pneumonia (%)	18 (31.6)	6 (100)	0.001

Note: The significant value $p \leq 0.05$ are in bold.

Abbreviations: ESC, European Society of Cardiology; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; LHD, left heart disease (diabetes mellitus, evidence of significant coronary artery, history of essential hypertension or body mass index > 30 kg/m²); PAH, pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance.

^aSymptomatic treatment (supportive care only): Antipyretics, analgesics, and mucolytics.

TABLE 1 Basal characteristics of PH patients and COVID-19 infection according to survival

DISCUSSION

This prospective study shows the experience in the management of COVID-19 in PH patients and the structural changes that took place in the PH network responsible for the care of the uninfected patients. The most relevant aspects are (1) Mortality was 9.5%, being higher in older patients with higher comorbidity burden; (2) The COVID-19 pandemic has led to a

significant change in patient care, both in the outpatient assessment and in the interventions that could be offered to PH patients. Referrals from other centers have decreased and outpatient activity has shifted toward a hybrid model with greater use of telemedicine. The impact of COVID-19 on interventions has mostly affected PTE, maintaining BPA procedures during most of the pandemic period, without differences in lung transplantation activity.

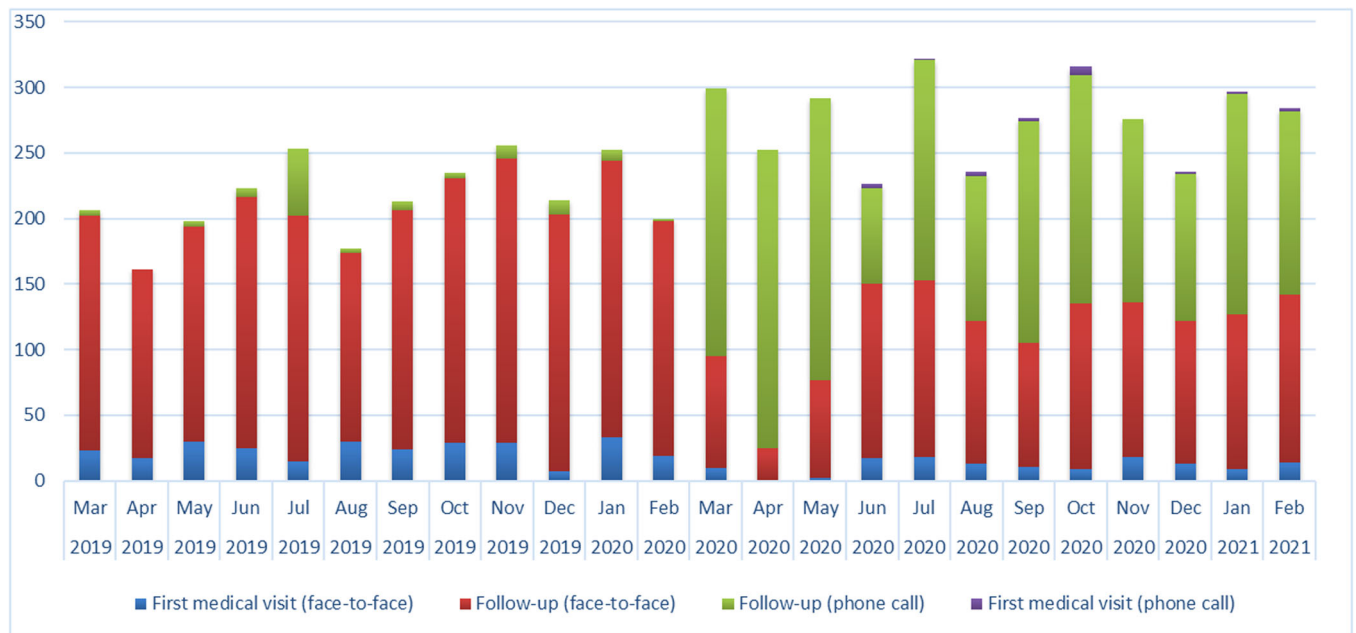


FIGURE 1 Monthly changes in medical consultation structure during the analyzed period

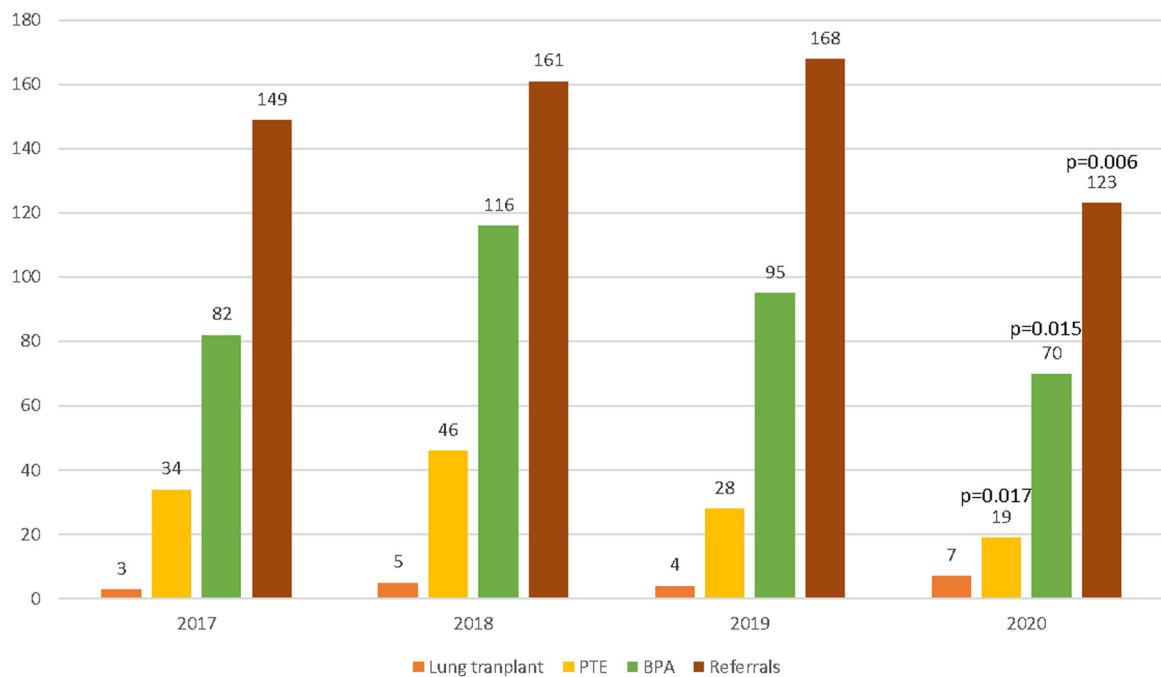


FIGURE 2 Yearly number of referrals and procedures comparing 2020 versus 3 prepandemic years. Significant value $p \leq 0.05$. BPA, balloon pulmonary angioplasty; PTE, pulmonary thromboendarterectomy.

Patients diagnosed with PAH/CTEPH and intercurrent COVID-19

In our patients with PAH/CTEPH, we observed a higher incidence of COVID-19 and lower overall mortality compared with other European and American series.¹⁰⁻¹³ We propose the following explanations for these findings:

a greater number of asymptomatic or mildly symptomatic cases diagnosed in our study, which is probably a consequence of the initially implemented strategies for early infection detection (patients information about symptoms and recommendation for urgent assessment upon onset of symptoms and disclosure through patients' associations), as well as easier access to the healthcare

team as a result of the relevant role of the specialized nurse in follow-ups and the promotion of email communication.¹⁴

The observed differences in COVID-19-related mortality between countries could be related to the different comorbidity burden between PH populations.¹⁵ Comorbidity has been shown to be a prognostic factor in the course of COVID-19 in the general population^{16–18} and appears to be one of the determinants of outcomes in patients with PH and intercurrent COVID-19.^{12,14} These data are consistent with our results, where patients with worse outcomes were older, with a higher Charlson index and a higher prevalence of risk factors associated with left ventricular dysfunction.

Surprisingly, the in-hospital mortality rate from COVID-19 in our PH patients was similar to that reported in the general population requiring admission.^{16,18} We expected a higher mortality rate such as the usually described during hospitalizations for noncardiovascular conditions in PH patients.²

However, in our cohort, those patients with severe hemodynamic profiles had a good outcome without heart failure or need for admission to an invasive care unit. Several hypotheses have been postulated to explain this: (1) Decreased angiotensin-converting enzyme 2 expression in PAH patients could act as a protective factor at an initial infective phase, avoiding virus entrance.^{19,20} (2) The basal lung perfusion abnormalities present in PAH patients could limit the abrupt perfusion imbalance towards nonventilated areas and limit the hypoxemia. (3) Associated vasodilator therapies limit the effects of endothelial dysfunction virus-induced.^{21,22} However, these theories are speculative. And more studies would be advisable for a better understanding of this phenomenon.

We, therefore, consider that outcomes after COVID-19 were more conditioned by the PH patient's comorbidity burden than their clinical condition, risk status, or hemodynamic profile. Accordingly, identifying PH patients with high comorbidity burden may deserve closer follow-up and early hospital admission.

Organization of care in the PH network

It is essential to highlight the decrease in referrals to the expert center from the network hospitals. This change could be due to the pressure on the national health service, with disruption in the referral system from primary care to medical specialists (mainly cardiologists or pneumologist)⁴ and consequently, the possibility of delay in diagnosis and treatment with an impact on the disease prognosis, which is yet to be determined.^{3,23}

The impact of COVID-19 on interventions has mostly affected PEA, probably because of the ineluctable need for ICU beds; while BPA procedures could be maintained during most of the pandemic period. This is probably because most CTEPH patients requiring BPA can stay in the cardiology ward, and when an ICU bed is required, it can be provided by the cardiology service itself, which in our institution is the one in charge of the coronary unit.

The telemedicine is an emergent tool with a potential usefulness for PH patients, but it is possibly inapplicable at all levels of the PH patient care. The evaluation and risk stratification process requires the assessment of multiple parameters, some of which cannot be addressed on the phone. Moreover, the reliability of using telemedicine may have limitations both related to patients such as the age or their educational level²⁴; as well as to the healthcare resources. Besides this, the pandemic has led to greater recognition of the specialized nursing, which contributes in two fundamental aspects: (1) follow-up of nonhospitalized patients with COVID-19 infection; (2) follow-up after initiation or titration of vasodilator drugs. The remote monitoring and telephone nurse coaching intervention to reduce readmissions among patients with chronic heart failure are well recognized.²⁵ Although their use is not yet that frequent in patients with PH, it has proved to be an invaluable tool in patient care.

Despite the limitations imposed by the pandemic, we could consider that the strategies used to continue the PH patients' care have shown encouraging results: The outpatient activity has been maintained, as well as that of the pulmonary transplant program and the BPA.

Vaccination is the cornerstone of prevention against COVID-19 infection. It has proven to be safe in PAH and CTEPH patients.²⁶ During the last pandemic wave due to the Omicron variant, we reported the highest incidence of all the pandemic period with 17 cases over one single month. Two of these patients were unvaccinated and only one of them required hospital admission.

Although we cannot give data about the percentage of immunized patients, since they were not within the study aims, in our population, the patients were highly receptive to vaccination. It is possible that the history of immunization against other infectious diseases such as influenza,²⁷ added to the acceptance by the Spanish population²⁸ could influence the positive attitude to vaccination. Therefore, we could consider that vaccination constitutes a safe, useful, and accessible preventive measure in patients with PH.

Despite a higher incidence of COVID-19 in our work compared to previous studies, there may still be an underreporting of cases due to the scant performance of diagnostic tests during the first pandemic wave and the

wide geographical distribution of our patients. However, we believe that closer contact with the patients and working closely with the treating physicians allowed us to gain real insight into PH patients during the pandemic. Another limitation is the small sample size and the low rate of events (six deaths during the period analyzed) could influence the external validity of the results and therefore, prevent us from obtaining more solid conclusions; however, it is the single-center registry with the largest number of cases of PAH/CTEPH and COVID-19.

CONCLUSIONS

In our experience, the outcomes of COVID-19 in PAH/CTEPH patients were related to age and comorbidities and unrelated to the hemodynamic or clinical status. The planned organization and distribution of resources made it possible to maintain the PH patients' care in our network. Recovery from referrals to specialized centers is critical because the poor prognosis associated with this disease changes dramatically when an early diagnosis and treatment can be offered.

AUTHOR CONTRIBUTIONS

Conceptualization: María José Cristo-Ropero, Williams Hinojosa, Pilar Escribano-Subias, Alejandro Cruz-Utrilla, Teresa Segura de la Cal. *Data curation:* María José Cristo-Ropero, Williams Hinojosa, Francisco López-Medrano, Rafael Salguero-Bodes, Begoña Navarro. *Formal analysis:* María José Cristo-Ropero, Williams Hinojosa, Alejandro Cruz-Utrilla, Teresa Segura de la Cal, Pilar Escribano-Subias. *Investigation:* Pilar Escribano-Subias, Carmen Pérez-Olivares, Begoña Navarro, Nuria Ochoa. *Methodology:* María José Cristo-Ropero, Williams Hinojosa, Alejandro Cruz-Utrilla, Pilar Escribano-Subias. *Resources:* Pilar Escribano-Subias, Fernando Arribas Ynsurriaga. *Software:* Alejandro Cruz-Utrilla, María José Cristo-Ropero. *Supervision:* María José Cristo-Ropero, Pilar Escribano-Subias. *Writing – original draft:* Williams Hinojosa, María José Cristo-Ropero. *Writing – review and editing:* María José Cristo-Ropero, Williams Hinojosa, Pilar Escribano-Subias, Alejandro Cruz-Utrilla, Teresa Segura de la Cal, Francisco López-Medrano, Rafael Salguero-Bodes, Carmen Pérez-Olivares, Fernando Arribas Ynsurriaga, Nuria Ochoa. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

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ETHICS STATEMENT

All patients signed the informed consent form according to the study protocol and to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by the institution's human research committee CEI N°:16/102 (April 20, 2016).

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