Five-year survival after an acute episode of decompensated pulmonary arterial hypertension in the modern management era of right heart failure

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To the Editor:

Acute decompensated pulmonary arterial hypertension (PAH) is characterised by rapid worsening of clinical signs of right heart failure (RHF) with subsequent congestion and systemic circulatory insufficiency that can lead to multisystem organ failure [1–3]. Short-term outcomes of acute decompensated RHF are very poor and it remains the primary cause of mortality in PAH [4, 5]. Intensive care of acute decompensated PAH is based on treatment of triggering factors, careful fluid management, and strategies to improve cardiac function and reduce right ventricular afterload [1]. However, this medical strategy is not always sufficient to restore a long-lasting balance between the afterload imposed on the right ventricle and its capacity for compensation. In case of refractory RHF despite maximal medical treatment, the use of mechanical support should now be considered in selected candidates for lung transplantation, or less commonly as a bridge to recovery in patients with a treatable cause of right-sided heart failure [1]. Veno-arterial extracorporeal membrane oxygenation (ECMO) is currently the most widely used strategy to support the right ventricle in PAH patients. This strategy, combined with changes in organ allocation rules to prioritise patients with a short-term life-threatening condition, should contribute to the improved survival of eligible patients with end-stage PAH [6]. However, long-term survival of patients admitted to the intensive care unit (ICU) for severe acute RHF management has not been studied extensively in the modern management era of mechanical support and high-priority lung transplantation.

In the present report, we describe the management and 5-year outcomes of consecutive PAH patients with acute RHF referred to the ICU of the French reference centre for pulmonary hypertension between February 2015 and February 2016. All patients were enrolled in the French PAH Registry and followed-up for a 5-year period. This retrospective study complied with the Declaration of Helsinki. Although French law does not require informed consent for retrospective data collection, the data collected were anonymised and complied with the requirements of the '*Commission Nationale Informatique et Libertés*', the organisation dedicated to privacy, information technology and civil rights in France. The committee approved the methods used to collect and analyse the data on 24 May, 2003 (approval number 842063).

Patients were divided into three age grades corresponding to tertiles, *i.e.* <50 years, 50–65 years and >65 years. Continuous variables were expressed as mean±SD. Categorical variables were expressed as number of patients and relative frequencies (percent). Overall survival time was defined from the date of ICU admission to death. Veno-arterial ECMO- and transplant-free survival was defined from the date of ICU admission to death, ECMO or transplantation. Surviving patients were censored at the date of last clinical contact. The Kaplan–Meier method was used to estimate the proportion of patients surviving at each time point up to 5 years post-ICU admission. Survival curves according to the three age grades were compared using the log-rank test. Univariable analysis based on the Cox proportional hazards model was used to examine the relationship between survival and selected variables at baseline and day 3.

70 patients (60% females, n=42) were enrolled in the study, with a mean age of 57±16 years at the time of ICU admission (n=24, 34%, in the <50 years age group; n=22, 32%, in the 50–65 years group; and n=24, 34%, in the >65 years group). According to the latest classification [7], 21 patients had idiopathic PAH

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(30%), two had heritable PAH (3%), five had drug-induced PAH (7%), 30 had PAH associated with another condition (43%) (connective tissue disease, n=15; HIV infection, n=2; portal hypertension, n=6; congenital heart disease, n=7) and 12 had PAH with overt features of venous involvement (pulmonary veno-occlusive disease) (17%). PAH diagnosis was revealed by the episode of acute decompensation in 20 patients (28%). At time of admission, 15 patients were treated with a monotherapy (21%), 21 with a dual combination (30%) and 14 with a triple therapy (20%). A parenteral prostacyclin analogue was included in the treatment regimen at admission in 16 patients (23%). A triggering factor was identified in 19 cases (27%) (infection, n=9; arrhythmia, n=4; postoperative, n=2; haemorrhage, n=3; treatment disruption, n=1). The value of the simplified acute physiology score at admission (SAPS II) was 22±9.

All were treated with intravenous diuretics and the use of inotropic support (dobutamine in all cases), and vasopressors (norepinephrine in all cases) were required in 46 (66%) and 23 (33%) patients, respectively. At time of admission, five patients were already listed for lung (LT) or heart–lung transplantation (HLT). In other patients <65 years old, eligibility for LT or HLT was systematically assessed, considering contraindications to transplantation defined in international recommendations [8]. The proportion of patients who were potentially eligible for LT or HLT was 71% and 27% in the <50 years age group and the 50–65 years group, respectively. Finally, 11 patients (16%) were transplanted with high priority organ allocation (national priority access to lung transplantation) including three patients aged 50–65 years. A veno-arterial ECMO was implanted in four awake patients under local anaesthesia as bridge to transplantation. One of them died in ICU before transplantation and three were transplanted 1 to 9 days after circulatory assistance initiation (figure 1a). After adjusting for age, creatinine at admission (HR 0.993, p=0.03), brain natriuretic peptide plasma levels at day 3 (HR 0.999, p=0.03) and mean arterial pressure (HR 1.044, p=0.009) at day 3 were associated with higher risk of ECMO implantation, urgent lung transplantation or death in ICU. Death in ICU was higher in patients with a triggering factor identified at time of admission (37% *versus* 14%; p=0.03).

Patients were not lost to follow-up. The rate of death at 3 months, 1 year and 5 years after ICU admission were 31%, 41% and 66% respectively (figure 1b). The overall survival at 5 years was significantly higher in the <50 years age group in comparison with the 50–65 and >65 years age groups (p=0.0004) (figure 1c): survival at 5 years in <50-year-old patients was 70%, while it was 23% and 12% in the 50–65 and >65 years age groups, respectively. In contrast, lung transplantation and ECMO-free survival was similar across the three age grades (figure 1d).

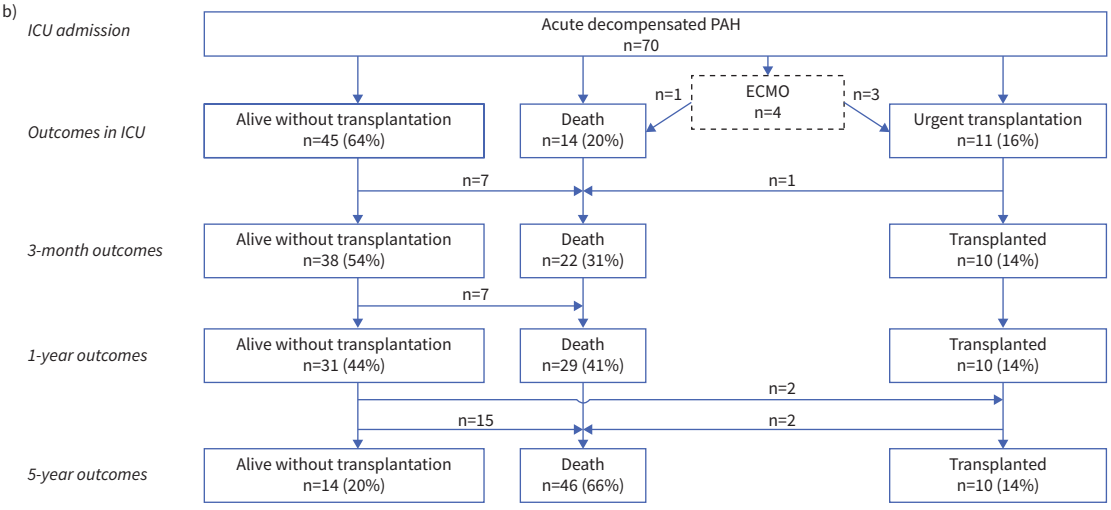
Our results show that acute decompensation of PAH remains a devastating life-threatening condition in the current management era. However, our data suggest recent improvements of short- and long-term outcomes in patients <50 years old, at least in part thanks to novel organ allocation rules, implementation of high-priority lung transplantation and use of ECMO as bridge to transplantation in eligible patients with refractory RHF. While event-free survival without ECMO and/or lung transplantation was similar in all age groups, the overall survival of <50-year-old patients was better than in older patients in our contemporary cohort (70% *versus* 23% and 12% in the 50–65 and >65 years age groups, respectively). In a previously reported cohort of patients admitted in the same ICU for acute PAH decompensation before the modern era of RHF management, the short-term survival at 3 months was similarly poor in all age groups (50%) [4]. At the time of our previous study, the time on the waiting list for lung transplantation was exceedingly long for a life-threatening condition and the use of ECMO was not yet generalised to the management of refractory RHF. These observations underscore that patients with acute decompensated PAH should be preferably managed in expert centres that are able to access all medical, interventional and surgical options including medical therapies, ECMO and lung transplantation, as emphasised by the 6th World Symposium on PH [1]. Most health systems have updated their lung allocation pathways with the implementation of scores and/or rules aiming to shorten the waiting time for the most advanced patients with an urgent need of high priority access to transplantation [6, 8, 9]. The possibility to offer high-priority lung transplantation to PAH patients with refractory RHF has led to a major reduction of waiting time and, by inference, reduced the risks of pre- and post-operative complications. The youngest patients have benefited more from this novel management approach. By contrast, refractory RHF in patients aged >50 years remains a dramatic life-threatening event in the evolution of the disease. Frequent comorbidities in these patients limit the access to an urgent transplantation. These results underline that fully evaluation for lung transplantation must be systematically considered early in the course of PAH in patients who do not reach a low risk profile with medical therapy, as proposed by the 6th World Symposium [1, 10]. The long-term outcomes of our cohort highlight that transplantation of outpatients in stable patients remains the best option.

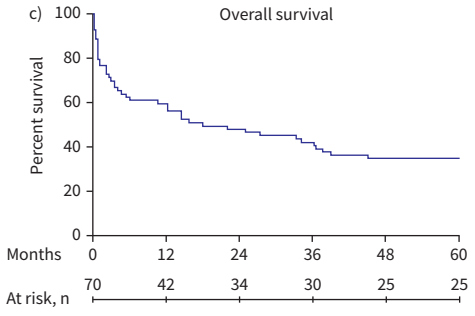
The main limitation of the present study is its monocentric nature. However, it should be highlighted that the French PAH reference centre hosts a dedicated pulmonary vascular disease ICU working in close

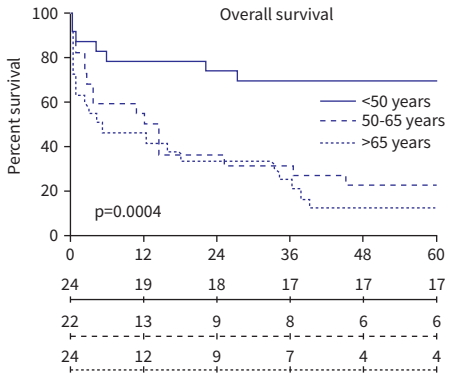
a) **Characteristics of patients who needed veno-arterial ECMO and/or urgent transplantation (n=12)**

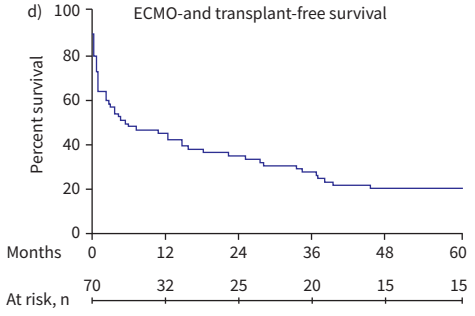
Age (years)	Sex	Type of PAH	PAH therapy at admission	On list at admission	Triggering factor	Inotropic support	Vaso-pressor	ECMO	Time in ICU before LT/HLT	Outcomes at 5 years
46	F	Idiopathic	Triple therapy#	No	No	Yes	Yes	Yes	23 days	Alive
55	M	Idiopathic	Triple therapy#	No	No	Yes	Yes	No	11 days	Death
20	M	Drug-induced	None	No	No	Yes	No	No	21 days	Alive
49	F	SSc	Oral dual therapy	Yes	Arrhythmia	Yes	Yes	Yes	2 days	Death
43	M	CHD	Triple therapy#	Yes	No	Yes	Yes	No	4 days	Alive
28	F	HIV	Triple therapy#	No	No	Yes	No	No	4 days	Alive
57	F	SSc	Oral dual therapy	Yes	No	Yes	Yes	No	15 days	Death
56	F	Drug-induced	None	No	No	Yes	Yes	No	14 days	Alive
17	F	Heritable	Triple therapy#	Yes	No	Yes	No	No	9 days	Alive
24	F	Heritable PVOD	Monotherapy	Yes	No	Yes	No	No	9 days	Alive
28	F	Idiopathic	Dual therapy#	No	No	Yes	Yes	Yes	7 days	Alive
50	M	Idiopathic	Triple therapy#	No	No	Yes	Yes	Yes		Death before LT

b)









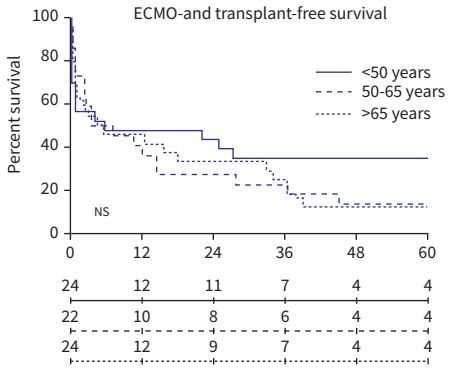


FIGURE 1 Outcomes after an acute episode of decompensated pulmonary arterial hypertension (PAH). a) Characteristics of patients who needed veno-arterial extracorporeal membrane oxygenation (ECMO) and/or urgent transplantation. #: including a parenteral prostacyclin analogue. b) Short- and long-term outcomes of patients admitted to the intensive care unit (ICU) for acute decompensated PAH. c) Overall survival. d) ECMO- and transplant-free survival. LT: lung transplantation; HLT: heart–lung transplantation; SSc: systemic scleroderma; CHD: congenital heart disease; PVOD: pulmonary veno-occlusive disease.

partnership with a nationwide network of 25 centres. We have followed country-specific lung allocation rules (High Priority Allocation Program) which may not apply to other institutions [6]. However, several countries have developed and refined lung allocation scores in order to prioritise the most severe patients at the time of listing and therefore reduce the risk of death on the waiting list [9, 11].

In conclusion, our data suggest that the implementation of novel medical, instrumental and surgical management of RHF translate to improvements in long-term survival of our youngest patients with acute decompensated PAH. Last, our data argue for management of such patients in expert centres with multidisciplinary teams able to offer all modern treatment options.

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