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Worsening in oxygen saturation and exercise capacity predict adverse outcome in patients with Eisenmenger syndrome

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ABSTRACT

Objectives: To evaluate (1) changes in clinical, biochemical and echocardiographic parameters, (2) whether deterioration in exercise capacity and resting oxygen saturation (SatO2-rest) are related with adverse outcome and (3) its additional value in predicting outcome in Eisenmenger patients.
Methods: Seventy-seven (36 ± 14 years, 30% male) patients were included and prospectively followed. Changes between baseline and final visit were evaluated. Clinical deterioration was defined as a deterioration in exercise capacity or SatO2-rest. Univariate and multivariate analyses were performed to evaluate predictors of outcome defined as the need for hospitalization due to right heart failure, transplantation, or all-cause mortality. Finally, the additional prognostic value of deterioration in exercise capacity and SatO2-rest was evaluated.
Results: During a mean follow-up period of 4.0 ± 2.1 years, 27 (35%) events occurred. Patients in the event-group presented with an deterioration in NYHA class ($P<0.0001$), 6 minute walk distance ($P=0.006$) and SatO2-rest ($P<0.0001$). After adjustment for baseline variables, multivariate Cox regression analysis indicated that clinical deterioration was independently associated with adverse outcome.
Conclusions: Clinical deterioration, defined as a deterioration in exercise capacity or SatO2-rest was associated with adverse outcome in Eisenmenger patients. Moreover, these parameters provided additional information on which patients would develop an event and may benefit from initiation or escalation of disease targeting therapy.

1. Introduction

Approximately 5–10% of patients with congenital heart disease develop pulmonary arterial hypertension of variable severity [1]. Eisenmenger syndrome, as first described by Dr. Paul Wood, represents a pathophysiological condition of pulmonary arterial hypertension associated with shunt reversal [2,3]. Several variables have been related with poor prognosis in this patient population, including complex congenital heart defect, higher New York Heart Association (NYHA) class, renal dysfunction, signs of right heart failure, a history of arrhythmias, iron depletion, and elevated brain natriuretic peptides [4–10]. Although Eisenmenger patients have lower annual mortality rates and a better prognosis when compared to patients with idiopathic pulmonary arterial hypertension, their life expectancy remains significantly reduced [5,6,8,11,12] and there is evidence of progression of pulmonary vascular disease over a time period as short as 16 weeks [13]. Disease targeting therapies have shown to increase exercise capacity and even improve survival in Eisenmenger patients [14].

According to the current pulmonary hypertension guidelines the need for starting or escalating disease targeting therapy in these patients requires knowledge of variables reflecting disease severity at a certain time point as well as variables reflecting disease progression and their relationship with clinical outcome. A practical table, including parameters with established importance in pulmonary hypertension, is included in the practice guidelines and defines treatment goals for these patients [15]. However, most of these target values are based on studies evaluating patients with idiopathic pulmonary arterial hypertension.

Therefore, this study aimed at evaluating (1) changes in clinical, biochemical and echocardiographic parameters during follow-up, (2) changes in exercise capacity and resting oxygen saturation (SatO2-rest) and their relation with adverse outcome and (3) the additional value of a deterioration in exercise capacity or in SatO2-rest in predicting adverse outcome in Eisenmenger patients.

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Table 1
Characteristics of patients presenting with or without an event at baseline and final visit.

	Baseline			Final visit		
	No-event group, $N=50$	Event group, $N=27$	*P*-value	No-event group, $N=50$	Event group, $N=27$	*P*-value
Age (years)	33±12	40±16	0.031	37±11*	43±16*	0.125
Male gender, *n* (%)	17 (34)	6 (22)	0.281	17 (34)	6 (22)	0.281
Down, *n* (%)	29 (58)	9 (33)	0.039	29 (58)	9 (33)	0.039
Diagnosis (%)	6/32/36/8	26/22/19/7	–	6/32/36/8	26/22/19/7	–
ASD/VSD/AVSD/PDA/Other	18	26		18	26	
Follow-up time (years)	4.4±2.0	3.3±2.3	0.034	4.4±2.0	3.3±2.3	0.034
Medication						
DTT (%)	76/24/0/0	52/33/15/0		72/20/4/4	26/48/11/15	
No/Mono/Double/Triple						
ERA, *n* (%)	11 (22)	12 (44)	0.040	14 (29)	17 (63)	0.004
PDE-5, *n* (%)	1 (2)	4 (15)	0.029	4 (8)	6 (22)	0.089
Prostacyclin, *n* (%)	0 (0)	1 (4)	0.171	2 (4)	3 (11)	0.247
Diuretics, *n* (%)	9 (18)	10 (37)	0.064	9 (18)	14 (52)	0.004
ACE-inhibitor/Sartan, *n* (%)	4 (8)	5 (19)	0.160	3 (6)	5 (18)	0.113
Beta-blocker, *n* (%)	3 (6)	3 (12)	0.396	5 (10)	3 (11)	0.975
Calcium antagonist, *n* (%)	2 (4)	2 (7)	0.494	0 (0)	2 (7)	0.061
Digoxin, *n* (%)	7 (14)	6 (22)	0.338	8 (16)	7 (26)	0.384
Antiplatelet drugs, *n* (%)	5 (10)	4 (15)	0.530	2 (4)	3 (11)	0.269
Anticoagulation, *n* (%)	5 (10)	10 (37)	0.004	5 (10)	12 (44)	0.001
Allopurinol, *n* (%)	11 (22)	7 (22)	0.666	16 (32)	11 (41)	0.611
Oxygen, *n* (%)	1 (2)	5 (19)	0.021	2 (4)	3 (11)	0.269
Phlebotomy, *n* (%)	8 (16)	10 (37)	0.037	9 (18)	7 (25)	0.558
Clinical parameters						
NYHA, *n* (1–4)	2/33/15/0	2/9/15/1	0.040	7/25/12/0	0/4/17/6*	<0.0001
NYHA ≥3, *n* (%)	15 (30)	16 (59)	0.012	12 (24)	23 (85)*	<0.0001
6MWD (m)	398±117	334±119	0.101	413±111	254±137*	0.001
6MWD<300 m, *n* (%)	4 (8)	11 (41)	0.125	3 (7)	16 (59)*	0.002
BMI (kg/m^2)	25±5	26±5	0.522	25±4	25±6	0.912
Syst BP (mm Hg)	114±14	125±21	0.006	112±14	113±28	0.839
Diast BP (mm Hg)	70±10	77±14	0.010	67±6	70±13	0.339
SatO2-rest (%)	84±7	84±7	0.807	84±7	78±9*	0.014
Biochemical parameters						
Hematocrit (%)	59±6	57±9	0.342	59±8	55±10	0.112
Hemoglobin (g/dL)	19.8±2.0	18.9±2.7	0.108	19.9±2.6	17.8±3.8	0.011
MCV (fL)	94±8	89±9	0.031	95±7	88±10	0.006
MCH (pg)	32±3	29±4	0.002	32±3*	29±4*	0.004
Platelets (×10^9/L)	161±54	168±67	0.648	141±53	159±66	0.234
Creatinine (mg/dL)	1.02±0.20	1.16±0.41	0.112	0.94±0.21	1.10±0.34	0.041
Uric acid (mg/dL)	6.5±1.9	7.5±2.6	0.077	6.0±2.0	7.0±3.0	0.226
Iron deficiency, *n* (%)	11 (22)	15 (56)	0.002	10 (20)	12 (44)	0.011
Echocardiographic parameters						
LA apical (mm)	43±9	49±10	0.008	43±10	50±10	0.007
RA apical (mm)	45±8	52±10	0.001	46±10	53±12	0.023
LV apical (mm)	39±10	37±8	0.452	38±8	36±6	0.190
RV apical (mm)	36±10	43±10	0.003	35±11	46±14*	0.001
LV EF (%)	64±9	65±1	0.585	66±10	62±13	0.217
RV function	1.4±0.6	2.2±0.8	<0.0001	1.4±0.6	2.5±1.0	<0.0001
TAPSE (mm)	18.5±4.0	16.0±4.1	0.024	20.3±4.8	15.1±3.9*	<0.0001
sPAP (mm Hg)	82±24	86±26	0.552	80±17	85±16	0.357

ASD: atrial septal defect; VSD: ventricular septal defect; AVSD: atrioventricular septal defect; PDA: patent ductus arteriosus; DTT: disease targeting therapy; ERA: endothelin receptor antagonist; PDE5: phosphodiesterase 5 inhibitor; NYHA: New York Heart Association; 6MWD: 6 minute walk distance: BMI: body mass index; SatO2-rest: resting oxygen saturation; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; LA: left atrium; RA: right atrium; LV: left ventricle; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion.
* $P<0.005$ change from baseline to final visit.

Patients with Eisenmenger physiology were recruited from the Belgian Eisenmenger registry, previously described [16]. Patients were prospectively followed in each centre with scheduled consultations, irrespective of clinical status. The study protocol conformed to the Declaration of Helsinki and the Institutional Review Board of each participating centre approved the registry and all patients gave written informed consent before inclusion. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Data collection at baseline

Demographic data, medical history (type of congenital heart defect, Down syndrome or not, surgical procedures, and non-cardiac history), clinical characteristics (NYHA class, blood pressure, body mass index, SatO2-rest, 6 minute walk distance), biochemical data and treatment were collected. Complex anatomy was defined as atrioventricular septal defect, transposition of the great arteries, truncus arteriosus and univentricular hearts.

NYHA classification was based on the 1994 revisions to the classification of functional capacity and objective assessment of patients with diseases of the heart [17]. Oxygen saturation was measured after 5 minutes of sitting on a bench with a transcutaneous oximeter placed on one of the fingers. In patients with patent ductus arteriosus, it was measured on the left hand. Iron deficiency was defined as ferritin <30 ng/mL or ferritine 30–100 ng/mL and a transferrin saturation <20% [6]. Standard 2D gray-scale and Doppler examinations were performed. Left ventricular function was assessed from parasternal two-dimensional M-mode measurements using Teichholz formula. In the apical 4-chamber view, the superior-inferior dimensions of the left atrium and right atrium at end-systole and the transverse dimensions of the left and right ventricle at end-diastole were measured. Right ventricular function was assessed qualitatively (on a scale from 1 = normal to 4 =

severely depressed right ventricular function) and quantitatively using tricuspid annular plane systolic excursion (TAPSE) from M-mode recordings. A TAPSE < 16 mm was considered as a decreased right ventricular function [9]. Systolic pulmonary artery pressure was obtained from Doppler recording using the modified Bernoulli equation (4 times tricuspid regurgitation peak systolic velocity squared).

2.3. Data collection during follow-up

Patient follow-up consisted of consecutive evaluations at a regular time basis of at least 6 months. At every visit, clinical and biochemical characteristics were evaluated. Transthoracic echocardiography was repeated every 6 or 12 months. The most recent evaluation or the evaluation before the occurrence of an end-point (death, hospitalisation due to right heart failure or transplantation) was considered the final visit.

2.4. Composite endpoint

In the registry, information on death, transplantation and the need for hospitalisation was included. The composite endpoint was defined as all-cause mortality, transplantation or hospitalisation due to right heart failure. Hospitalizations for the initiation or escalation of disease targeting therapy were excluded.

2.5. Statistical analysis

Data were analysed using SPSS® for Windows (version 19, SPSS, Chicago). The Kolmogorov–Smirnov test was used to test normality. Descriptive data for continuous variables are presented as means ± SD or as medians with ranges when appropriate. Descriptive data for discrete variables are presented as frequencies or percentages.

In a first step, changes in variables were evaluated using a paired-t test for continuous variables or a McNemar test for proportions, with Bonferroni correction for multiple testing.

In a second step, subgroups (event vs no-event group) were compared using an independent student *t*-test or a Mann–Whitney *U* test for continuous variables or a Chi-square test for proportions. The rate of decrease in SatO2-rest was calculated as the difference between the baseline value and the value at the final visit, divided by the time interval in years. In order to obtain a clinical meaningful variable, clinical deterioration was defined as a rate of decrease in SatO2-rest ≥ 75th percentile, an increase in NYHA class or a decrease in 6 minute walk to a value below 300 m.

In a third step, uni- and multivariate Cox-regression analysis was performed with the composite endpoint as a dependent variable. Patients were censored after the first event. Clinical deterioration was corrected for baseline variables: "age at inclusion, iron deficiency, right ventricular function and disease targeting therapy". Disease targeting therapy was included in the Cox regression model as a time dependent variable in order to account for therapy started during follow-up. The level of significance for the multivariate model was set at 0.05.

In the last step, we evaluated the additional value of a deterioration in exercise capacity or SatO2-rest for risk stratification. Risk factors at baseline included NYHA ≥ 3, right ventricular dysfunction (TAPSE < 16 mm) and iron deficiency. Deterioration was defined as patients with an increase in NYHA *or* a 6 minute walk distance < 300 m *or* a decrease in SatO2-rest ≥ 75th percentile. Kaplan–Meier analysis and the log-rank test were performed.

3. Results

3.1. Patient characteristics

Seventy-seven Eisenmenger patients (mean age 36 ± 14 years; 30% male) were included, 10 with atrial septal defect, 23 with atrioventricular septal defect, 22 with ventricular septal defect, 6 with a patent ductus arteriosus and 16 with other underlying heart defects. Patient characteristics at baseline and at the final visit for the entire cohort are summarized in Table 1.

Although patients with an event during follow-up were more intensively treated at baseline and were more likely to receive add-on therapy during follow-up, a significant increase in NYHA class ($P<0.0001$), a decrease in 6 minute walk distance ($P=0.006$) and a decrease in SatO2-rest ($P<0.0001$) were observed in the event group. There was no significant change in right ventricular function ($P=0.078$) or renal function ($P=0.429$).

Between-group comparison indicated that patients in the event group had a higher NYHA class at baseline and at the final visit when compared to patients in the no-event group. Six-minute walk distance at the final visit was significantly lower in the event group when compared to the no-event group. Patients in the event group were more likely to be iron deficient. Although SatO2-rest was not different at baseline, patient in the event group had a lower SatO2-rest at the final visit. Despite the lower SatO2-rest, these patients had lower hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin values than patients in the no-event group. Right ventricular function at baseline and at the final visit was lower in the event than in the no-event group (Table 1).

The absolute decrease and the rate of decrease in SatO2-rest were higher in the event than in the no-event group. Moreover, a greater proportion of patients increased NYHA class during follow-up in the event-group (Table 2). Fig. 1 shows a progressive decrease in SatO2-rest in the event-group whereas it remains stable in the non-event group.

3.2. Variables related with outcome in univariate analysis

During a mean follow-up period of 4.0 ± 2.1 years, 27 (35%) events occurred. Thirteen (17%) patients died, 2 (3%) underwent transplantation and 21 (27%) were hospitalized during follow-up. Variables related with adverse outcome in univariate analysis are summarized in Table 3.

3.3. Variables related with outcome in multivariate Cox regression analysis

After adjustment for age, the need for disease targeting therapy and iron deficiency, multivariate Cox regression analysis indicated that clinical deterioration was independently related with adverse outcome (HR 4.26; 95%CI 1.62–11.14; $P=0.003$)

In a subgroup of patients (without complex congenital heart disease), after adjustment for age, the need for disease targeting therapy and right ventricular function, multivariate Cox regression analysis indicated that clinical deterioration was independently related with adverse outcome (HR 4.67; 95%CI 1.60–13.68; $P=0.005$) (Table 4).

3.4. Additional value of deterioration in exercise capacity or SatO2-rest in the evaluation of Eisenmenger patients

Based on differences in baseline parameters between the event and no-event group, 3 risk factors were identified: NYHA class ≥ 3, right ventricular dysfunction and iron deficiency. An increasing number of risk factors *at baseline* was related with a lower event-free survival when compared to patients without risk factors (Fig. 2). Clinical deterioration (determined from significant changes during follow-up in the event-group: increase from NYHA ≤ 2 to ≥ 3 *or* a 6 minute walk distance to a value < 300 m *or* a decrease in SatO2-rest ≥ 2% per year) was added. Kaplan–Meier analysis indicated a stepwise increase in the event rate with additional risk factors present. Moreover, there were no events in the group of patients without risk factors (Fig. 3). In order to evaluate the impact of the model on all-cause mortality, Fig. 4 shows that an increasing number of risk factors was also related with higher mortality.

4. Discussion

This prospective study indicated that a deterioration in exercise capacity and SatO2-rest was related with adverse outcome in Eisenmenger patients, irrespective of treatment status or baseline

Table 2
Decrease in SatO2-rest and decrease in NYHA class between baseline and final visit.

	Total population, $N=77$	No event group, $N=37$	Event group, $N=34$	*P*-value
Absolute decrease in SatO2-rest (%)	2.1 ± 6.1	0.0 ± 59	5.5 ± 4.7	<0.0001
Rate of decrease in SatO2-rest (%/year)*	0.5 (−0.7; 2.0)	0.0 (−1.1; 1.0)	2.2 (0.4; 7.6)	<0.0001
Increase in NYHA class, *n* (%)	15 (21)	5 (11)	10 (37)	0.010

SatO2-rest: resting oxygen saturation; NYHA: New York Heart Association.
* Median with interquartile range, between-group comparison with Mann–Whitney *U* test.

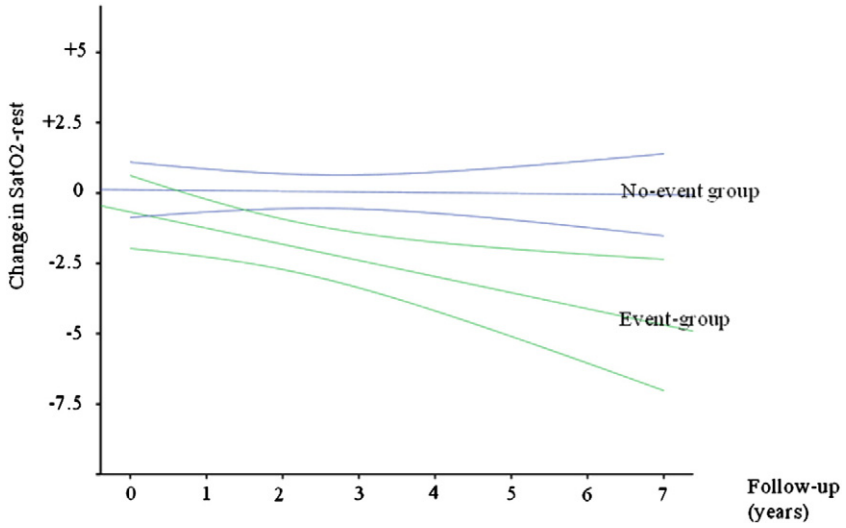


Fig. 1. In the event-group there is a progressive decrease in SatO2-rest, whereas SatO2-rest remains stable in the no-event group (plot indicates group mean with mean confidence interval).

risk factors. Moreover, this study demonstrated that deterioration provided more accurate information on which patients were at risk to develop an event during follow-up, as compared to baseline parameters alone.

4.1. Changes in variables related with adverse outcome

Several clinical variables have been related with poor prognosis in Eisenmenger patients, including higher NYHA class, renal dysfunction, signs of right heart failure, a history of arrhythmias, iron depletion and elevated brain natriuretic peptides [4–10,18,19]. However, little is known about the relationship of changes in clinical variables with outcome in Eisenmenger patients. Our results indicated that an increase in NYHA during follow-up is related with adverse outcome, even after correction for baseline variables, including disease targeting therapy. Although initiation of disease targeting therapy improves the proportion of patients in NYHA class 1 or 2, changes in NYHA have only been related with outcome in patients with idiopathic pulmonary arterial hypertension [20]. Therefore, our results confirm the current practice guidelines that an increase in NYHA warrants the need for starting or escalation of disease targeting therapy in these patients. Although not available in all patients, a decrease in 6 minute walk distance to a value <300 m was related with worse outcome. Six minute walk distance has been related with worse outcome [10], but a change in 6 minute walk distance was not yet been related with outcome. Until now, SatO2-rest in Eisenmenger patients was not unequivocally related with outcome [10]. Interestingly, Diller et al. recently showed that initiation or escalation of disease targeting therapy in Eisenmenger patients improved oxygen saturation at peak exercise, providing a possible explanation for the improvement in 6 minute walk distance with disease targeting therapy [13,21]. Our study indicated that a decrease in SatO2-rest is also related with adverse outcome even after adjustment for baseline variables and concomitant disease targeting therapy. Although a decrease in SatO2-rest can be explained by many factors, including changes in systemic vascular resistance and filling pressures, progressive pulmonary vascular disease should be considered in these patients [13]. Right ventricular dysfunction has important prognostic significance in patients with pulmonary arterial hypertension, including Eisenmenger patients [9,22] and there have been reports suggesting that disease targeting therapy may improve right ventricular function [23]. Although right ventricular function was worse in patients with events, there was no apparent change in TAPSE during follow-up.

Table 3
Univariate Cox regression analysis of variables related with adverse outcome defined as a composite endpoint of all-cause mortality, hospitalization due to right heart failure or transplantation.

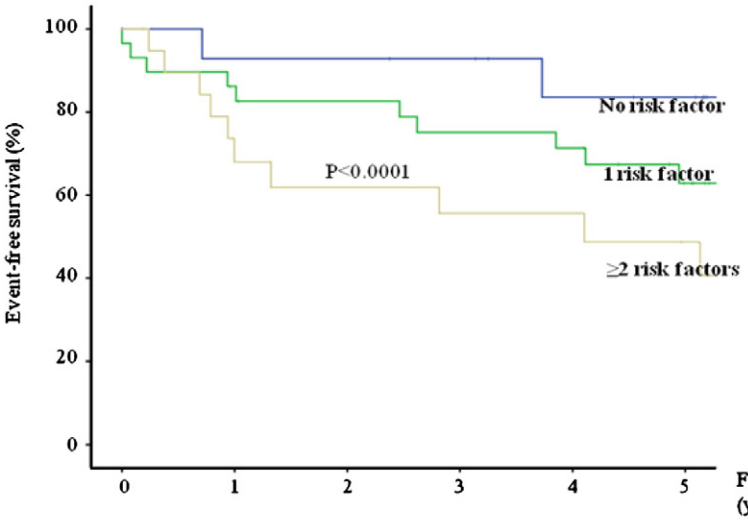
Variable	Hazard ratio (95%CI)	*P*-value
Age (years)	1.03 (1.00–1.06)	0.033
Male gender	0.750 (0.30–1.88)	0.540
Down syndrome	2.08 (0.92–4.72)	0.080
Complex defect	1.53 (0.97–2.42)	0.067
DTT	1.58 (1.11–2.24)	0.010
NYHA≥3	2.42 (1.11–5.28)	0.027
6MWD <300 m	2.53 (0.98–6.49)	0.054
SatO2-rest (%)	1.01 (0.96–1.06)	0.768
MCV (fL)	0.93 (0.88–0.97)	0.002
MCH (pg)	0.81 (0.73–0.90)	<0.0001
Iron deficiency	3.99 (1.66–9.60)	0.002
LA apical (mm)	1.06 (1.02–1.11)	0.004
RA apical (mm)	1.09 (1.05–1.14)	<0.0001
RV function	2.59 (1.60–4.21)	<0.0001
TAPSE (mm)	0.88 (0.80–0.98)	0.020
Clinical deterioration	1.60 (1.06–2.41)	0.002

DTT: Disease targeting therapy; 6MWD: 6 minute walk distance; NYHA: New York Heart Association class; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; LA: left atrium; RA: right atrium; RV: right ventricular; TAPSE: tricuspid plane annulus systolic excursion. Clinical deterioration defined as increase in NYHA class, rate of decrease in SatO2-rest ≥2% per year.

Table 4
Multivariate Cox regression analysis of variables related with adverse outcome defined as a composite endpoint of all-cause mortality, hospitalization due to right heart failure or transplantation. (A) Clinical deterioration was corrected for age, the need for disease targeting therapy and iron deficiency. (B) Clinical deterioration was corrected for age, the need for disease targeting therapy and right ventricular function in a subgroup excluding patients with complex congenital heart defect.

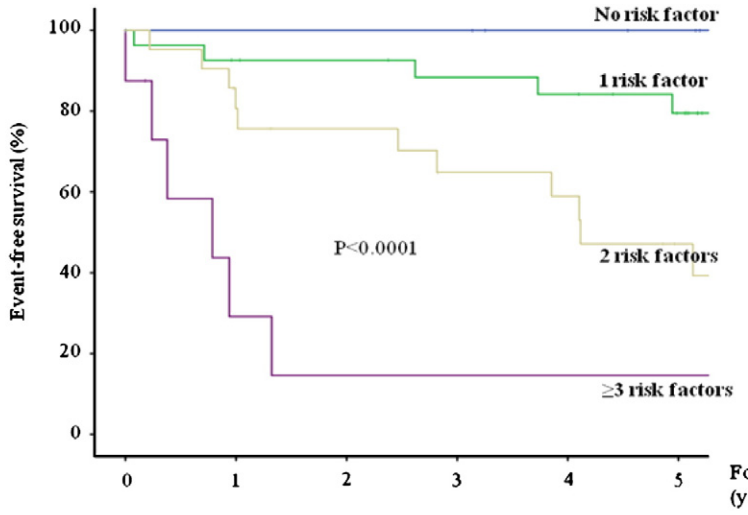
Variable	Hazard ratio (95%CI)	*P*-value
A.		
Age (years)	1.01 (0.98–1.04)	0.653
DTT	1.39 (0.93–2.07)	0.107
Iron deficiency	2.93 (1.05–8.21)	0.041
Clinical deterioration	4.25 (1.62–11.14)	0.003
B.		
Age (years)	1.02 (0.99–1.04)	0.219
DTT	1.42 (1.00–2.01)	0.051
TAPSE<16 mm	0.86 (0.20–3.66)	0.864
Clinical deterioration	4.67 (1.60–13.68)	0.005

DTT: Disease targeting therapy. Clinical deterioration defined as increase in NYHA class, rate of decrease in SatO2-rest ≥2% per year.



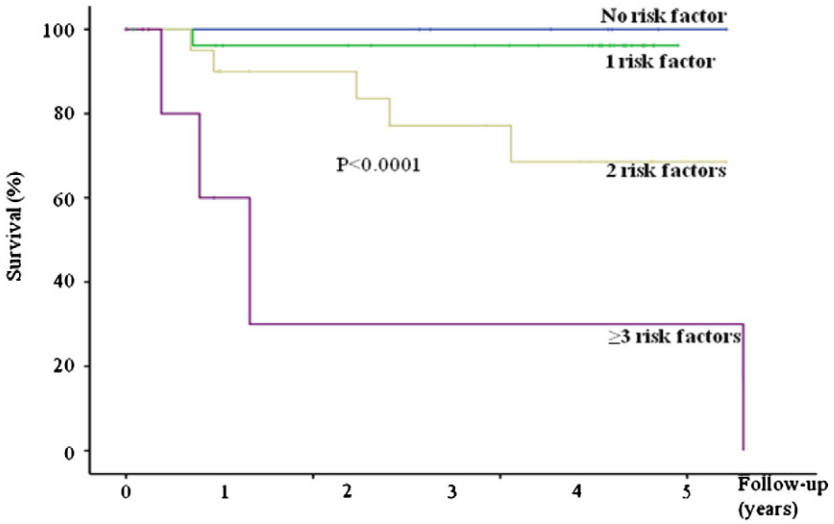
No risk factor	Numbers at risk	16	13	13	12	9	8
	Number of events	0	1	1	1	2	2
1 risk factor	Numbers at risk	29	24	22	20	19	13
	Number of events	0	4	5	7	8	10
≥2 risk factors	Numbers at risk	21	12	10	8	8	6
	Number of events	0	6	7	8	8	9

Fig. 2. Kaplan–Meier plot indicating event-free survival according to the number of risk factors present at baseline. Risk factors included the presence of NYHA≥3, right ventricular dysfunction defined as TAPSE<16 mm and iron deficiency.



No risk factor	Numbers at risk	9	7	7	7	5	4
	Number of events	0	0	0	0	0	0
1 risk factor	Numbers at risk	27	24	23	21	20	16
	Number of events	0	2	2	3	4	5
2 risk factors	Numbers at risk	22	16	14	11	10	6
	Number of events	0	4	5	7	8	10
≥3 risk factors	Numbers at risk	8	2	1	1	1	0
	Number of events	0	5	6	6	6	7

Fig. 3. Kaplan–Meier plot indicating event-free survival according to the number of risk factors evaluated at baseline and during follow-up. In addition to baseline risk factors (NYHA≥3, iron deficiency and right ventricular dysfunction), clinical deterioration (defined as an increase in NYHA class from ≤2 to ≥3, a decrease in 6 minute walk distance to <300 m or a rate of decrease in SatO2-rest ≥2% per year) was considered.



No risk factor	Numbers at risk	9	7	7	7	6	4
	Number of events	0	0	0	0	0	0
1 risk factor	Numbers at risk	27	24	23	21	20	16
	Number of events	0	1	1	1	1	1
2 risk factors	Numbers at risk	22	15	14	11	10	6
	Number of events	0	2	2	4	5	5
≥3 risk factors	Numbers at risk	8	2	1	1	1	1
	Number of events	0	2	3	3	3	4

Fig. 4. Kaplan–Meier plot indicating event-free survival according to the number of risk factors evaluated at baseline and during follow-up.

4.2. Additional value of deterioration, defined as deterioration in exercise capacity or SatO2-rest in predicting adverse outcome of ES patients

Several studies have indicated a symptomatic improvement in Eisenmenger patients with bosentan [24–27]. The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) and the 6 month open-label extension study indicated a beneficial effect of bosentan in NYHA 3 Eisenmenger patients [13,28]. More recently, studies including NYHA 2 and 3 Eisenmenger patients indicated that phosphodiesterase-inhibitors may also improve exercise capacity [29–32]. The only study including exclusively mildly symptomatic (NYHA 2) patients with pulmonary arterial hypertension (but which only included a subgroup of patients with pulmonary arterial hypertension associated with congenital heart disease(17%)) suggested a beneficial effect of bosentan [33].

When evaluating exercise capacity using cardiopulmonary exercise testing and considering a strict definition of NYHA class, virtually all Eisenmenger patients should be classified in NYHA class 2 [34–36]. However, Eisenmenger patients often report a better than expected perceived health and it has been shown that there is a lack of consistency in classification between clinicians [37,38]. Nevertheless, NYHA remains a powerful prognostic tool even in Eisenmenger patients as it is the often the only parameter evaluating exercise capacity [37]. Moreover, assessing changes in variables may be important predictors of outcome as they specifically confer to deterioration of a parameter in a single patient.

In this study, we consecutively evaluated the ability to predict an event using baseline parameters only and baseline parameters in combination with parameters reflecting deterioration of patients. Baseline risk factors have been described before [9] and appear complementary with a higher risk in patients with more risk factors present. Importantly, we were able to demonstrate that risk stratification combining baseline and follow-up variables is superior to that based on baseline variables alone, with sensitivity and specificity improving the more risk factors are present. The current study may help in clinical decision making, especially guiding the decision to start or escalate disease targeting therapy. The use of NYHA ≥ 3 or increase in NYHA during follow-up to start or escalate disease targeting therapy is a close reflection of current clinical practice and is supported by the current evidence [15]. If patients fall below 300 m in their 6 minute walk distance their prognosis appears impaired, suggesting the need to intensify treatment. Finally, as disease targeting therapy is able to increase oxygen saturation [21], a patient with a deterioration in SatO2-rest may benefit from the initiation or escalation of disease targeting therapy.

5. Limitations

First, due to the nature of the condition, the number of patients was relatively low. However, the data was sufficient to perform the appropriate statistics. Second, not all patients had information on iron status, TAPSE or 6 minute walk distance at baseline and follow-up, which would have provided additional prognostic information. Third, neither laboratory nor echocardiographic data were analyzed in a core laboratory, which may have influenced standardisation of results. Fourth, values of SatO2-rest were only obtained at baseline and at the final visit. Therefore, one cannot be sure that SatO2-rest decreases linearly. Fifth, data for the study was obtained through the Belgian Adult Congenital Heart Disease registry. As only patients who gave written informed consent were included in the study, a selection bias may be present. Finally, data on BNP-values or NT-proBNP values were not available in the registry.

6. Conclusions

A deterioration in exercise capacity and SatO2-rest is related with adverse outcome in Eisenmenger patients. Moreover, the deterioration in exercise capacity and SatO2-rest ≥2% per year provided additional information on which patients would develop an event during follow-up and therefore may benefit from initiation or escalation of disease targeting therapy.

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