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Prognosis value of Forrester's classification in advanced heart failure patients awaiting heart transplantation

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Abstract

Aims The value of Forrester's perfusion/congestion profiles assessed by invasive catheter evaluation in non-inotrope advanced heart failure patients listed for heart transplant (HT) is unclear. We aimed to assess the value of haemodynamic evaluation according to Forrester's profiles to predict events on the HT waitlist.

Methods and results All non-inotrope patients ($n = 837$, 79% ambulatory at listing) registered on the French national HT waiting list between 1 January 2013 and 31 December 2019 with right heart catheterization (RHC) were included. The primary outcome was a combined criteria of waitlist death, delisting for aggravation, urgent HT or left ventricular assist device implantation. Secondary outcome was waitlist death. The 'warm-dry', 'cold-dry', 'warm-wet', and 'cold-wet' profiles represented 27%, 18%, 27%, and 28% of patients, respectively. At 12 months, the respective rates of primary outcome were 15%, 17%, 25%, and 29% ($P = 0.008$). Taking the 'warm-dry' category as reference, a significant increase in the risk of primary outcome was observed only in the 'wet' categories, irrespectively of 'warm/cold' status: hazard ratios, 1.50; 1.06–2.13; $P = 0.024$ in 'warm-wet' and 1.77; 1.25–2.49; $P = 0.001$ in 'cold-wet'.

Conclusions Haemodynamic assessment of advanced HF patients using perfusion/congestion profiles predicts the risk of the combine endpoint of waitlist death, delisting for aggravation, urgent heart transplantation, or left ventricular assist device implantation. 'Wet' patients had the worst prognosis, independently of perfusion status, thus placing special emphasis on the cardinal prominence of persistent congestion in advanced HF.

Keywords Advanced heart failure; Forrester's classification; Heart transplant; Cardiac oedema; Cardiovascular diseases

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Introduction

Heart failure (HF) is a general health burden affecting 1–2% of the adult population in Western countries.¹ Advanced heart failure is defined by the severity of symptoms and the instability of clinical status despite optimized treatment, ultimately leading to substantial rates of congestive, rhythmic or low-output episodes.² Heart transplant (HT) remains the reference treatment for advanced HF patients. Risk stratification of these high-risk patients is of major importance given organ shortage leading to a sizeable waiting time after transplant listing.

In 1976, Forrester *et al.* described four haemodynamic profiles by the combined evaluation of pulmonary capillary wedge pressure (PCWP) and cardiac index (CI).^{3,4} The ‘cold’ feature refers to low cardiac index, whereas the ‘wet’ feature corresponds to elevated capillary wedge pressure. These four ‘Forrester’ profiles (i.e. warm/cold × dry/wet) were emphasized as useful in the 2021 European Society of Cardiology (ESC) HF guidelines in context of acute heart failure using bedside physical examination.³ Whether Forrester’s profiles are useful in a population of advanced heart failure patients that share certain characteristics with acute HF patients has not been assessed.

The aim of the present study is to describe and assess the prognostic value of Forrester’s profiles in non-inotrope patients with advanced HF listed for HT.

Methods

Study population

A total of 2089 newly registered adult patients (18 years or older), without previous solid organ transplants (heart, kidney, liver, or pancreas) listed on the French national waiting list for heart transplantation between 1 January 2013 and 31 December 2019 were deemed eligible. Of the latter, 1000 patients without indication for combined transplantation, intravenous inotrope, mechanical assistance, or dialysis at time of listing were included. One hundred sixty-three patients were excluded from further analysis due to the lack of right heart catheterization or missing cardiac index or PCWP values. Overall, the cohort included 837 non-inotrope advanced heart failure patients with right heart catheterization, CI, and PCWP evaluation allowing a classification according to Forrester’s profiles.

Right heart catheterization

Cardiac catheterization measurements constituted part of the assessment process for heart transplant listing in order to estimate pulmonary vascular resistance. Cardiac catheterization

data were registered prospectively at time of transplant listing. Haemodynamic variables obtained during catheterization included systolic blood pressure (mmHg), diastolic blood pressure (mmHg), cardiac index (l/min/m²), pulmonary capillary wedge pressure (mmHg), pulmonary vascular resistance (Wood unit), and mean pulmonary arterial pressure (mmHg).

Forrester’s classification

Patients were allocated in four groups according to PCWP and CI. ‘warm-dry’ was defined by CI > 2.0 l/min/m² and PCWP < 20 mmHg; ‘cold-dry’ by CI ≤ 2.0 l/min/m² and PCWP < 20 mmHg; ‘warm-wet’ by CI > 2.0 l/min/m² and PCWP ≥ 20 mmHg; and ‘cold-wet’ by CI ≤ 2.0 l/min/m² and PCWP ≥ 20 mmHg, according to 2021 ESC guideline values to assess eligibility for implantation of a left ventricular device.¹

Follow-up and study outcomes

The primary outcome was a combined criteria of the occurrence of waitlist death, delisting for aggravation, urgent heart transplantation, or left ventricular assist device implantation stratified by congestion/hypoperfusion classification. Secondary outcomes were components of the primary outcome.

A new system based on a score ranking all candidates was implemented in January 2018 resulting in the dropping of high-urgency status.⁵ Urgent heart transplant was defined by the use of intravenous inotrope or extracorporeal mechanical assistance at the time of transplant. For all analysis, patients were censored at time of non-urgent transplant or delisting for improving medical condition. Delisting for worsening medical condition was left at the discretion of the clinician and considered as an outcome in the primary analysis but as a censoring for the analysis of individual events such as urgent transplant, survival, and left ventricular assist device implantation.

Data collection and variables

This national multicentre study was performed using the data of the French registry (CRISTAL). The registry is administered by the Ministry of Health (*Agence de la Biomédecine*), which prospectively collects data on all organ transplant candidates in France along with their outcomes. A description of the CRISTAL registry has previously been published.⁶ Data were registered in CRISTAL at the time of patient listing and during follow-up as part of routine care. The study was conducted according to French legislation stipulating that anonymized research studies based on the national CRISTAL registry do not require institutional review board or ethic approval.

Statistical analysis

All results were first summarized overall and subsequently stratified according to the four Forrester's profiles and thereafter dichotomized between ambulatory and hospitalized patients.

Baseline continuous variables are expressed as medians with interquartile 25–75% (IQ_{25–75}) range or as means (\pm standard deviation). Comparisons of continuous variables were carried out using the Kruskal–Wallis test and *t* test as required. Categorical variables are expressed as frequencies (percentages) and compared using the χ^2 test. The two-tailed significance level was set at $P < 0.05$. Due to the use of BNP or N terminal pro brain natriuretic peptide (NTproBNP) depending on the collection year and centres, a combined BNP or NTproBNP Z-score value was created.

Outcomes were stratified according to Forrester's classification. Primary outcome was assessed and illustrated by Kaplan–Meier analyses. After graphically verifying the assumption of proportional hazard model, multivariable Cox proportional hazard regression was used to examine the association between Forrester's profile and primary and secondary outcomes. The ensuing multivariable model was adjusted for baseline characteristics (age and gender) and laboratory variables known to be associated with outcome in advanced heart failure (total bilirubin, estimated glomerular filtration rate and BNP, or NTproBNP Z-score). In the first multivariable model (Model 1), associations were adjusted for age, gender, and estimated glomerular filtration rate. In order to further evaluate the added value of the Forrester's profile on top of other congestion variables, a second model (Model 2) was further adjusted on total bilirubin and BNP or NTproBNP Z-score.

All analyses were performed using SPSS version 27.0.1.0 (IBM SPSS Statistics for Windows, NY, USA: IBM Corp).

Results

Baseline characteristics

Among the 837 studied patients (median age 55 years, 70% men), 79% were ambulatory at time of listing, 45% had dilated cardiomyopathy and 30% had ischaemic cardiomyopathy (Table 1). Median HF duration was 7.0 years, a minority of patients had comorbidities (20% hypertension and 15% diabetes). Patients had severe left ventricular systolic dysfunction with a median ejection fraction of 25% and a left ventricular end-diastolic diameter of 64 mm. Median BNP, NTproBNP, and estimated glomerular filtration rate (eGFR) were 681 ng/L, 2590 ng/L, and 63 mL/min/1.73 m², respec-

tively. Overall, cardiac index was severely reduced (2.1 L/min/m²), and mean pulmonary artery pressure and pulmonary capillary wedge pressure were increased with values of 29 and 20 mmHg, respectively. Pulmonary vascular resistance was normal (2.0 Wood units).

Forrester's profile characteristics

'Warm-dry', 'Cold-dry', 'Warm-wet', and 'Cold-wet' profiles represented 27%, 18%, 27%, and 28% of cases, respectively. Medical characteristics such as hypertension, smoking history, heart failure duration, cardiac resynchronization therapy, or implantable cardioverter defibrillator were not significantly different between groups (Table 1). Furosemide equivalent dose, NTproBNP and total bilirubin levels significantly varied according to Forrester's profile with 'cold-wet' > 'warm-wet' > 'cold-dry' > 'warm-dry' (Table 1). CI, PCWP, mean pulmonary artery pressure, and pulmonary vascular resistance were significantly different among groups ($P < 0.001$) and are presented in Table 2.

Outcomes on waitlist

Overall, 'wet' patients had the worst prognosis whereas 'dry' patients (independently of perfusion status) experienced best outcome. At 12 months, death on waitlist mortality occurred in 3.2%, 3.4%, 4.8%, and 6.5% for 'warm-dry', 'cold-dry', 'warm-wet', and 'cold-wet' profiles, respectively. At 12 months, waitlist death, delisting for aggravation, urgent heart transplantation, or left ventricular assist device implantation occurred in 35 (15.2%), 25 (16.8%), 56 (24.7%), and 66 (28.6%) for 'warm-dry', 'cold-dry', 'warm-wet', and 'cold-wet' patients, respectively. Of the patients 440 (53%) were transplanted without intravenous inotrope or extracorporeal mechanical assistance at time of transplant. 'Wet' patients had the worst prognosis irrespective of perfusion status (Figure 1), $P = 0.008$ for log-rank test. The patients who did not have haemodynamic data available were not significantly different from the patients included in the main analysis except for heart failure duration, furosemide equivalent dose and implantable cardioverter defibrillator prevalence (Supporting information Table S1).

Similarly, other waiting list events increased gradually according to the Forrester's classification with 'warm-dry' < 'cold-dry' < 'warm-wet' < 'cold-wet'. Waitlist mortality or urgent heart transplant and waitlist mortality, urgent heart transplant or LVAD implantation occurred in 13.0%, 15.4%, 20.7%, and 23.8% ($P = 0.037$ for log-rank test) and in 13.0%, 16.8%, 22.5%, and 26.0% ($P = 0.007$ for log-rank test) for 'warm-dry', 'cold-dry', 'warm-wet', and 'cold-wet' patients, respectively.

Table 1 Patient characteristics, medication use, laboratory, and echocardiographic parameters at time of heart transplant listing according to Forrester's classification

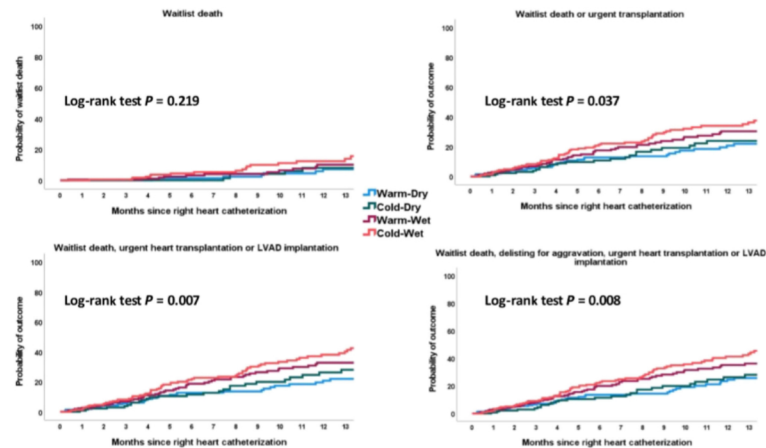
	Missing (%)	Whole cohort n = 837	Warm-dry n = 230 (27%)	Cold-dry n = 149 (18%)	Warm-wet n = 227 (27%)	Cold-wet n = 231 (28%)	P value
Ambulatory							
Hospitalized	0	664 (79)	183 (80)	127 (85)	183 (81)	171 (74)	0.061
		173 (21)	47 (20)	22 (15)	44 (19)	60 (26)	
Demographic data							
Delay between RHC and inscription on HT waiting list, days	8 (1)	53 (20-108)	59 (20-119)	51 (22-105)	57 (23-106)	40 (17-100)	0.144
Age, years	0	55.3 (46.0-61.1)	55.7 (47.7-62.2)	56.5 (44.3-61.5)	55.2 (46.0-61.0)	53.5 (44.2-59.8)	0.165
Male sex, n (%)	0	590 (70)	154 (67)	98 (66)	171 (75)	167 (72)	0.117
Medical history							
Hypertension, n (%)	24 (3)	164 (20)	36 (16)	31 (21)	48 (21)	49 (22)	0.393
Diabetes, n (%)	0	129 (15)	33 (14)	16 (11)	47 (21)	33 (14)	0.050
Smoking history, n (%)	25 (3)	463 (57)	115 (52)	83 (57)	135 (60)	130 (59)	0.274
Heart failure duration, days	0	2,538 (507-5,516)	2,211 (461-5,201)	3,504 (664-5,822)	2,446 (439-6,867)	2,478 (610-5,104)	0.275
Heart failure aetiology, n (%)							
Ischaemic, n (%)	0	252 (30)	74 (32)	35 (23)	68 (30)	75 (32)	0.469
Dilated cardiomyopathy, n (%)	0	377 (45)	98 (43)	74 (50)	97 (43)	108 (47)	
Hypertrophic cardiomyopathy	0	82 (10)	21 (9)	18 (12)	21 (9)	22 (10)	
Rejection	0	2 (0)	1 (0)	1 (0)	0	0	
Other, n (%)	0	124 (15)	36 (16)	21 (14)	41 (18)	26 (11)	
Furosemide equivalent dose, mg	11 (1)	120 (40-250)	80 (40-243)	80 (40-250)	125 (60-300)	125 (60-375)	<0.001
CRT, n (%)	57 (7)	254 (30)	64 (30)	48 (32)	77 (36)	65 (31)	0.509
ICD, n (%)	11 (1)	701 (84)	183 (81)	127 (85)	193 (85)	198 (88)	0.213
Biological data							
Creatinine, µmol/L	1 (0)	104 (86-130)	103 (83-127)	98 (86-129)	105 (86-126)	110 (89-137)	0.051
eGFR, mL/min/1.73 m ²	1 (0)	62.9 (49.3-82.0)	65.1 (51.1-81.8)	67.3 (47.8-84.1)	62.8 (52.0-82.3)	60.2 (46.3-80.8)	0.192
Natremia, mmol/L	2 (0)	137 (135-139)	138 (135-140)	138 (135-140)	137 (135-139)	137 (134-139)	0.010
Total bilirubin, µmol/L	25 (3)	13 (9-20)	12 (8-19)	13 (9-18)	14 (10-20)	15 (10-23)	<0.001
BNP, ng/L	591 (71)	681 (361-1,186)	436 (219-998)	565 (347-1,181)	843 (497-1,351)	922 (501-1,607)	<0.001
NTproBNP, ng/L	294 (35)	2,590 (1,467-4,760)	2,010 (1,039-3,635)	2,396 (1,029-4,354)	2,729 (1,505-4,757)	3,821 (1,853-6,460)	<0.001
BNP/NTproBNP Z-score	62 (7)	-0.28 (-0.35-0.19)	-0.442 (-0.642-0.067)	-0.35 (-0.63-0.10)	-0.23 (-0.50-0.22)	-0.04 (-0.45-0.52)	<0.001
Echocardiography							
LVEF, %	19 (2)	35 (20-30)	25 (20-31)	27 (20-40)	25 (20-30)	21 (20-28)	<0.001
LVEDD, mm	184 (22)	64 (56-73)	63 (55-73)	61 (51-71)	67 (59-75)	66 (58-73)	0.005

BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HT, heart transplant; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NTproBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; RHC, right heart catheterization. Values are expressed as median (interquartile₂₅₋₇₅) or n (%). Other heart failure aetiologies included restrictive, congenital, familial, valvular cardiomyopathies, myocarditis, and cardiac neoplasia.

At listing time	Missing (%)	Whole cohort n = 837	Warm-dry n = 229	Cold-dry n = 149	Warm-wet n = 227	Cold-wet n = 231	P value
Haemodynamic variables							
Mean PAP, mmHg	2 (0)	29 (22–36)	22 (18–26)	20 (16–24)	35 (30–40)	34 (30–40)	<0.001
PCWP, mmHg	0	20 (15–26)	14 (11–17)	14 (10–17)	25 (22–29)	26 (23–30)	<0.001
CI, L/min/m ²	0	2.1 (1.7–2.4)	2.4 (2.2–2.7)	1.8 (1.5–1.9)	2.4 (2.2–2.7)	1.7 (1.5–1.9)	<0.001
PVR, Wood units	13 (2)	2.0 (1.4–2.8)	1.8 (1.1–2.3)	2.1 (1.4–3.0)	2.0 (1.4–2.7)	2.4 (1.8–3.5)	<0.001
Clinical and functional variables							
Systolic blood pressure, mmHg	70 (8)	101 (93–111)	102 (95–112)	100 (92–110)	104 (95–112)	100 (91–109)	0.022
Diastolic blood pressure, mmHg	69 (8)	65 (60–73)	65 (59–72)	65 (60–74)	67 (60–74)	65 (60–72)	0.611
NYHA I	5 (1)	5 (1)	2 (1)	1 (1)	1 (0)	1 (0)	0.790
NYHA II		87 (10)	23 (10)	16 (11)	21 (9)	27 (12)	
NYHA III		571 (69)	159 (70)	109 (73)	155 (68)	148 (65)	
NYHA IV		169 (20)	43 (19)	23 (15)	50 (22)	53 (23)	
VO ₂ max	269 (30)	12.5 (10.2–15.0)	12.6 (10.3–15.6)	12.6 (10.5–15.0)	12.9 (10.5–15.0)	12.0 (10.0–14.8)	0.269

CI, cardiac index; IV, intravenous; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

Figure 1 Likelihood of different outcomes according to Forrester's profiles.



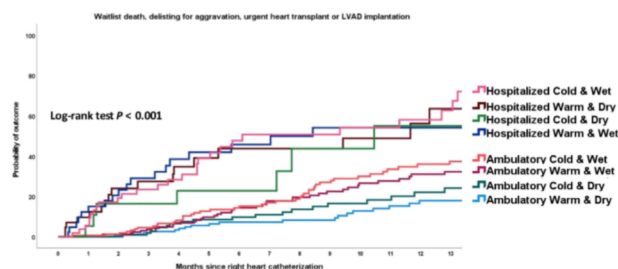
Impact of hospitalization status

Hospitalized patients had worse outcome irrespective of congestion/perfusion status, $P < 0.001$ for log-rank test (Figure 2). The association of congestion/perfusion profile with the primary outcome was not significantly different across hospitalized and ambulatory patients (P for interaction >0.05).

Clinical and haemodynamic predictors of waitlist death

The 'cold-wet' profile had a trend for an increased risk of waitlist death in univariable analysis [hazard ratio (HR), 1.96; 95% confidence interval (CI), 0.95–4.05, $P = 0.069$] (Table 3) but not after adjustment.

Figure 2 Likelihood of waitlist death, delisting for aggravation, urgent heart transplantation, or left ventricular assist device (LVAD) implantation according to Forrester's profiles and hospitalization status.



Clinical and haemodynamic predictors of waitlist outcomes

In crude analyses, significant associations with outcomes on waitlist were observed only for wet profiles, irrespectively of the perfusion status. The 'warm-wet' profile was associated with a 77% increase in the primary outcome of the study [waitlist death, delisting for aggravation, urgent heart transplant, or left ventricular assist device (LVAD) implantation] (HR, 1.77; 95% CI, 1.25–2.49; $P = 0.001$) whereas the 'cold-wet' was associated with a 50% increase in this outcome (HR, 1.50; 95% CI, 1.06–2.13; $P = 0.024$) (Figure 3). In contrast, cold and dry profiles were not significantly associated with considered outcomes.

When adjusting for age, gender and eGFR at listing (Model 1), the association with primary outcome remained significant for both warm-wet and cold-wet profiles (Table 3). When further adjusting for other congestion variables (total bilirubin and NTproBNP—Model 2), cold-wet patients experienced the worst outcome, with a 73% increased risk of primary outcome (HR, 1.73; 95% CI, 1.18–2.53; $P = 0.005$). The 'warm-wet' profile remained significantly associated with the primary outcome (HR, 1.54; 95% CI, 1.05–2.27; $P = 0.029$) whereas the cold-dry profile only tended to be associated with the primary outcome (HR, 1.53; 95% CI, 0.98–2.37; $P = 0.061$) (Table 3).

Sensitivity analysis

When considering only New York Heart Association (NYHA) III/IV patients (i.e. excluding NYHA II patients) the association of Forrester profile with outcome was similar [waitlist mortality ($P = 0.296$); waitlist mortality or urgent heart transplant ($P = 0.039$); waitlist mortality, urgent heart transplant, or

LVAD implantation ($P = 0.008$); waitlist mortality, delisting for aggravation, urgent heart transplant, or LVAD implantation ($P = 0.016$)].

Discussion

In this national prospective cohort of heart transplant waiting list patients with haemodynamic assessment, we demonstrate that Forrester's profiles are associated with waitlist death, delisting for aggravation, urgent heart transplantation, or assist device implantation in non-inotrope advanced heart failure patients while accounting for other clinical and laboratory criteria. Overall, wet patients, regardless of their output status, experienced the worse outcome. Interestingly, low-output patients (most of whom were ambulatory—approximately 75%) did not consistently have an increased risk of waitlist mortality, delisting for aggravation, urgent heart transplant, or LVAD implantation in the absence of congestion.

Relevance of Forrester's classification in acute and advanced heart failure

Forrester's classification was initially described in a population of cardiogenic shock patients in 1976^{3,4} and based on a haemodynamic evaluation. In 2003, Nohria *et al.* described the value of congestion and perfusion assessment in a population of advanced heart failure patients.⁷ However, only 17% of the patients were admitted for elective heart transplant evaluation and the majority were hospitalized for acute decompensation (49%), arrhythmia (12%), or angina (12%). Importantly, in contrast with Forrester's initial publication, congestion and perfusion were evaluated clinically. In their study,

Table 3 Adjusted association of Forrester's profiles with outcomes

	Warm-dry	Cold-dry	Warm-wet	Cold-wet
Model 1 adjusted on age, gender, and eGFR at listing				
Waitlist mortality	Reference	1.20 (0.50-2.90) <i>P</i> = 0.686	1.21 (0.55-2.64) <i>P</i> = 0.635	1.80 (0.87-3.72) <i>P</i> = 0.116
Waitlist mortality or urgent heart transplant	Reference	1.21 (0.76-1.94) <i>P</i> = 0.420	1.43 (0.95-2.14) <i>P</i> = 0.087	1.66 (1.12-2.48) <i>P</i> = 0.012
Waitlist mortality, urgent heart transplant, or LVAD implantation	Reference	1.37 (0.88-2.15) <i>P</i> = 0.168	1.67 (1.14-2.46) <i>P</i> = 0.009	1.80 (1.23-2.65) <i>P</i> = 0.003
Waitlist mortality, delisting for aggravation, urgent heart transplant or LVAD implantation	Reference	1.23 (0.81-1.86) <i>P</i> = 0.326	1.49 (1.05-2.12) <i>P</i> = 0.025	1.68 (1.19-2.38) <i>P</i> = 0.003
Model 2 adjusted on age, gender, eGFR, BNP, or NTproBNP Z-score and total bilirubin at listing				
Waitlist mortality	Reference	1.37 (0.55-3.43) <i>P</i> = 0.504	1.08 (0.46-2.53) <i>P</i> = 0.862	1.54 (0.70-3.42) <i>P</i> = 0.284
Waitlist mortality or urgent heart transplant	Reference	1.42 (0.87-2.32) <i>P</i> = 0.165	1.36 (0.87-2.13) <i>P</i> = 0.172	1.55 (1.01-2.40) <i>P</i> = 0.047
Waitlist mortality, urgent heart transplant or LVAD implantation	Reference	1.63 (1.02-2.61) <i>P</i> = 0.041	1.59 (1.05-2.42) <i>P</i> = 0.030	1.77 (1.17-2.68) <i>P</i> = 0.007
Waitlist mortality, delisting for aggravation, urgent heart transplant or LVAD implantation	Reference	1.53 (0.98-2.37) <i>P</i> = 0.061	1.54 (1.05-2.27) <i>P</i> = 0.029	1.73 (1.18-2.53) <i>P</i> = 0.005

'wet-warm' and 'wet-cold' patients had a worse prognosis compared with 'warm-dry' patients with respective hazard ratios of 2.23 and 2.73⁷ for heart transplantation or death. Moreover, this previous report included only 16 patients (3.5%) classified as 'dry-cold' rendering any statistical analysis inconclusive.⁷

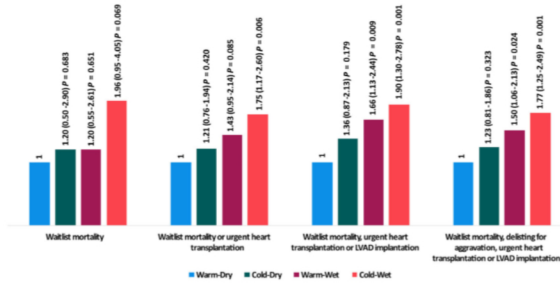
More recently, the 2016 and 2021 ESC Heart Failure guidelines promoted the use of Forrester's classification in acute HF to guide therapy at the initial phase as well as add prognostic information.^{1,8} Chioncel *et al.* assessed the value of this classification in acute HF patients from the ESC-EORP-HFA Heart Failure Long-Term Registry.⁹ Similarly, 'cold and dry' patients accounted for only 0.4% of the total population at admission and 1.6% at discharge.

Our study adds new and useful data on the prognostic value of haemodynamic profiling in advanced HF. First, we were able to demonstrate the value of this classification in non-inotrope-dependent advanced heart failure patients treated with contemporary HF drugs whether they were ambulatory or hospitalized (no heterogeneity between ambulatory/hospitalized profile in light of a non-significant *P* value for interaction). Second, while the proportion of 'cold-dry' profile was low, our findings show that it represented at least 18% of patients waiting for heart transplant. Discordance between clinical and haemodynamic evaluation has been reported in numerous advanced or acute HF studies,^{10,11} leading to an underestimation of the 'cold-dry' profile (which is actually fairly frequent in our cohort). Our study suggests that low-output status is a rather frequent condition in patients listed for HT even in ambulatory setting (as less than 25% of low-output patients were hospitalized).

Congestion or perfusion for prediction of events in advanced HF patients

Persistence of clinical congestion at discharge in patients hospitalized for acute HF has been acknowledged as a risk factor for HF hospitalization and mortality in many studies.^{9,12} In the present study, congestion assessed by PCWP ≥ 20 mmHg was associated with the risk of primary outcome (waitlist death, delisting for worsening medical condition, urgent heart transplantation or LVAD implantation) in non-inotrope-dependent patients listed for heart transplant. To the best of our knowledge, this is the first study to provide contemporary data on the deleterious impact of PCWP elevation in patients awaiting heart transplantation. Interestingly, this association between PCWP and outcomes remained significant after adjustment for gender, age, renal function, peptide natriuretic, and bilirubin. These results are in concordance with the results of a study by Stevenson *et al.* showing that patients referred for heart transplantation who were unable to normalize filling pressure during tailored therapy were at higher risk of death.¹³ Similarly, patients from the Escape trial with elevated

Figure 3 Crude association of Forrester's profiles with outcomes. LVAD, left ventricular assist device.



pressure at discharge were also found at higher risk of combined risk of death, cardiovascular hospitalization, and transplantation (HR, 2.03; 95% CI, 1.31–3.15, $P < 0.01$).¹⁴

In contrast with the results related to congestion, the impact of hypoperfusion on heart transplant waitlist mortality is unclear. In a study by Morley *et al.* in 1994, univariate but not multivariate association between cardiac output and 1 year mortality was observed.¹⁵ In a recent meta-analysis comprised of 18 studies, most of which were published prior to drug treatments of the current era, no association was reported after adjustment between cardiac index and prognosis.¹⁶ In our study, the Cold-Dry profile only tended to be associated with the primary outcome after adjustment on biological variable related to congestion (natriuretic peptide and total bilirubin), which intrinsically disadvantage other congestion variables (such as PCWP). Our findings further confirm the lack of firm association between cardiac index and prognosis in a much more contemporary HF population, especially in non-congestive patients. Indeed, only the congestion aspect of the Forrester classification provided prognostic information. The lack of impact of cardiac index on cardiac outcomes in the current study is, to some extent, in keeping with the studies on inotrope therapy, which failed to improve prognosis in advanced heart failure.^{17–19}

Implications for clinical practice

In a position statement on advanced heart failure from the Heart Failure Association,²⁰ right heart catheter parameters were not listed as risk markers in patients with advanced heart failure and none of the prognostic scores proposed in this position statement included haemodynamic assessment (Heart Failure Survival Score, Seattle Heart Failure Model,

Metabolic Exercise test data combined with Cardiac and Kidney Indexes, Meta-Analysis Global Group in Chronic Heart Failure).^{21–24} In the advanced heart failure population, right heart catheterization is part of the assessment process prior to waitlist inscription, although it typically does not participate in the risk stratification of these patients. Results of the present study suggest that special focus on PCWP should be devoted to further enhance risk stratification. Moreover, neither Eurotransplant nor US allocations systems uses PCWP in allocation scores.⁵ Given the demonstration herein that Forrester's classification is associated with outcome in addition to other risk markers such as age, gender, eGFR, total bilirubin, and NTproBNP or BNP, further consideration to Forrester's profiles in allocation systems may be useful.

Prospective studies are needed to assess whether PCWP normalization (i.e. decongestion) could improve outcome in patients on the heart transplant waiting list. If congestion becomes an actionable target of advanced HF management, repeated assessment of congestion could prove useful. Non-invasive methods such as lung ultrasound, inferior vena cava quantification, renal venous ultrasound, and jugular vein Doppler have been shown to be strongly associated with outcome in HF.^{25,26} As congestion appears similarly important in advanced HF patients, this non-invasive quantification of congestion, in particular lung ultrasound which is correlated with pulmonary pressure,²⁷ could be of particular interest. Two studies using either lung ultrasound or pulmonary artery pressure (PAP) monitoring to assess congestion have shown their utility in guiding HF therapy with a reduction in HF urgent visits or hospitalization.^{28,29} These findings were however not confirmed in a haemodynamic-guided HF study, although this latter study was impacted by the COVID-19 pandemic.³⁰

Our results also raise another concern regarding the place of diuretics in advanced heart failure. Association between high loop diuretic dose and prognosis has been reported in

numerous studies.^{31,32} Whether the elevated loop diuretic dose was simply a marker of disease severity or could be associated with side effects remains unclear. Congestive patients were also treated with higher doses of loop diuretic in the present study. Cardiorenal syndrome and diuretic resistance could explain the failure to reach PCWP normalization despite the increase in diuretic dose. Experts recommend the use of intravenous loop diuretic or adding a second class of diuretic in this setting.^{33,34} In a recent study by Cox *et al.*, metolazone, IV chlorothiazide, or tolvaptan added to loop diuretics showed excellent weight loss without significant differences between treatments.³⁵ However, most studies on diuretic strategies or diuretic resistance focus on acute settings; whether these treatment strategies are feasible or useful in chronic conditions remains unclear, and further studies are needed, particularly in ambulatory populations.

Limitations

Several limitations in the present study should be highlighted. First, only non-inotrope patients without mechanical assistance who had available right heart catheterization at time of listing were included in our analysis; these criteria likely excluded the most severe patients. However, right heart catheterization interpretation is difficult in patients with haemodynamic instability and/or treated by intravenous inotrope venoarterial extracorporeal membrane oxygenation (VA-ECMO)/LVAD. NYHA Stage II patients were included in our analysis; according to 2021 ESC-HF guidelines, patients with NYHA Stage II dyspnoea and another characteristic (such as systolic blood pressure <90 mmHg, >1 admission or unplanned visit to HF clinic within last 12 months, and prior inotropic use) are defined as 'advanced heart failure patients'. Importantly, analyses performed only in NYHA III–IV patients yielded similar results than in the whole cohort. Second, this is an observational study, and causality cannot be ascertained. Third, congestion and perfusion were only assessed by haemodynamic evaluation without symptoms data, leading to a different profile distribution compared with 'clinical evaluation' studies. Nevertheless, this weakness also represents a strength because haemodynamic congestion was found to be associated with poor prognosis regardless of symptoms. Fourth, data regarding treatments during follow-up were not available. Whether the treatments of cold status (i.e. inotropes and VA-ECMO) have mitigated its prognostic significance of cold status cannot be evaluated. However, the 2021 European Society of Cardiology HF guidelines¹ do not recommend treating patients based on haemodynamic values at right heart catheterization without a context of clinical or biological hypoperfusion. It seems unlikely that intravenous inotropes or VA-ECMO were introduced in the setting of ambulatory low cardiac output.

Conclusions

Haemodynamic assessment using Forrester's profiles of advanced HF patients is associated with clinical outcome on heart transplant waiting list. Wet patients exhibited the worst prognosis, independently of perfusion status.

Clinical perspectives and translational outlook portion of your manuscript

Clinical perspectives

Right heart catheter parameters is not listed as risk markers in patients with advanced heart failure and none of the prognostic scores routinely used. As in the advanced heart failure population, right heart catheterization is part of the assessment process prior to waitlist inscription, our results suggest that PCWP can further enhance risk stratification. Further consideration to Forrester's profiles in allocation systems may be useful. In addition, our results also highlight the importance of diuretics/congestion in advanced heart failure. Whether congestion treatment optimization based on right heart catheter parameters in the specific setting of pre-transplant patients would improve outcome is yet to be evaluated.

Translational outlook portion of your manuscript

Mechanistic studies are needed to determine why PCWP is associated with outcome in advanced heart failure patients. We do not know the biological profile of these patients, even if Bio-adrenomedullin has been emphasized recently as a key biological feature.³⁶ This lack of translational evidence is surprising given the central place of congestion in HF. A better understanding of the pathophysiology of congestion could actually lead to the discovery of new therapeutic targets.

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Conflict of interest

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