

A Retrospective Multicentre Evaluation of the Outcomes and Management of Carcinoid Heart Disease in Patients with Advanced Midgut NETs: A NET-CONNECT Descriptive Study

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Introduction: Carcinoid heart disease (CHD) is a poor prognostic factor in neuroendocrine tumours (NETs). However, the extreme variability of diagnostic and treatment approaches reported in literature account for uncertainties on the best management in this selected population.

Aims: To evaluate the clinical management of patients with advanced midgut NET who developed CHD and correlate clinico-pathological parameters to overall survival (OS).

Materials and methods: A multicentre retrospective cohort study in patients with midgut NET diagnosed with CHD by echocardiography (EC) (2008-2018). OS was calculated from the time of CHD diagnosis to the date of death or last follow-up. Survival curves were estimated using the Kaplan-Meier method. Univariate and multivariable hazard ratios were estimated using Cox regression models.

Results: A total of 136 patients were included. At the time of NET diagnosis there were 91% of patients with signs of carcinoid syndrome and 47% with CHD (Tab. 1). During the disease course 53% developed CHD (median 2.4 years), 80% showed moderate / severe tricuspid insufficiency at EC. Valve surgery was performed in 32% patients. The median (m) OS after diagnosis of CHD was 2.4 years (Fig. 1) and 2.8 following valve surgery. By univariate analysis OS was influenced by valve surgery (HR 0.39 95% CI 0.24-0.62, p<0.001), high NTproBNP (>3 xULN) (HR 1.89 95% CI 1.04-3.43, p=0.038) (Tab. 2). Valve surgery and NTproBNP retained statistical significance after multivariable analysis.

Table 1. Patient and tumour characteristics

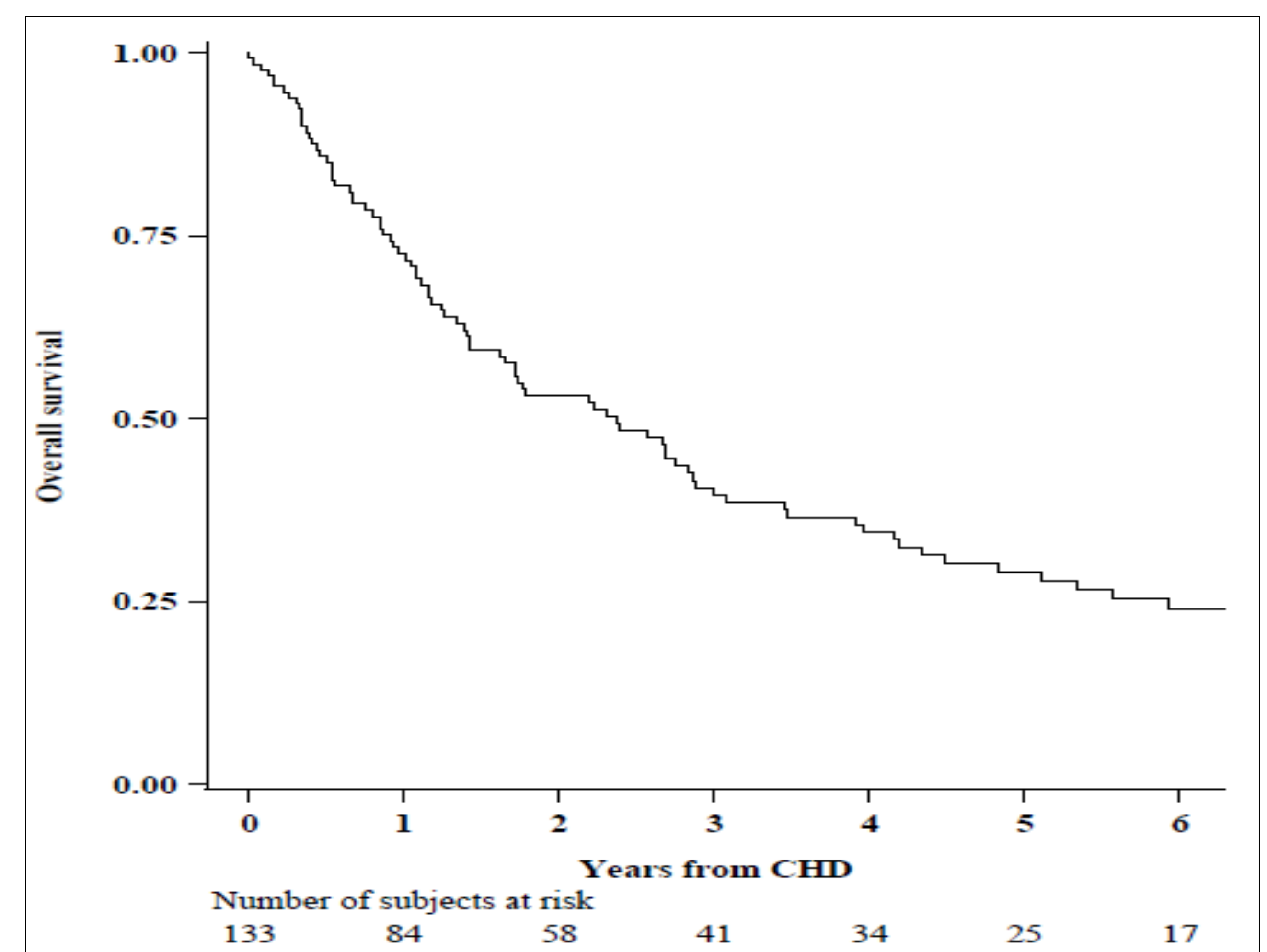
Variable	Level	Overall (N=136)	Variable	Level	Overall (N=136)
Age at diagnosis of CHD, median (min-max)		65 (38-89)	At diagnosis of SI-NET		
Gender, N (%)	Female	68 (50.0)	Liver metastases, N (%)	No	4 (3.0)
	Male	68 (50.0)		Yes	131 (97.0)
PS (ECOG) at diagnosis, N (%)	0	51 (45.1)		Missing	1
	1	55 (48.7)	Ki-67 (highest value obtained at all sites), median (min-max)		4 (0.5-25)
	2	7 (6.2)		Missing	22
	Missing	23	Morphology, N (%)	Well differentiated	131 (100.0)
CS at diagnosis of SI-NET, N (%)	No	12 (8.8)		Missing	5
	Yes	124 (91.2)	USHIAA *, median (min-max)		27.5 (1-100)
Symptoms of CS, N (%)	None	5 (3.8)		Missing	69
	Flushing	19 (14.3)	Prior to CHD diagnosis		
	Diarrhoea	33 (24.8)	SSA, N (%)	No	35 (26.1)
	Both	76 (57.1)		Yes	99 (73.9)
	Missing	3		Missing	2

Table 2. Association between patients and disease characteristics and death (univariate models) (N=133 *)

Variable	Level	N	Death / PY	Rate x 100 PY	2-y OS	HR	95% CI	P-value
Overall		133	88/362	24.3	53.1 (43.7-61.7)			
Age at diagnosis of CHD	≤65 □	66	34/228	14.9	62.5 (48.3-73.8)	Ref.		
	>65	67	54/134	40.3	44.5 (32.0-56.3)	2.31	1.49-3.58	<0.001
Valve surgery	No	90	62/169	36.7	39.6 (28.5-50.5)	Ref.		
	Yes	43	26/193	13.5	78.0 (62.1-87.9)	0.39	0.24-0.62	<0.001
Ki-67	≤4 □	64	40/199	20.1	62.3 (48.5-73.4)	Ref.		
	>4	48	33/93	35.5	38.0 (23.5-52.5)	1.62	1.02-2.58	0.042
	Missing	21	15/69					
PRRT prior to CHD	No	97	63/301	20.9	56.9 (45.9-66.4)	Ref.		
	Yes	35	25/61	41.0	40.8 (22.9-58.1)	1.68	1.05-2.68	0.032
Interferon prior to CHD	No	126	83/356	23.3	54.4 (44.7-63.0)	Ref.		
	Yes	6	5/5	100	22.2 (1.0-61.5)	3.15	1.25-7.94	0.015
	Missing	1	0/0					
NTproBNP at CHD **	≤3 □	31	24/88	27.3	54.5 (35.5-70.0)	Ref.		
	>3	28	21/37	56.8	33.8 (15.6-53.0)	1.89	1.04-3.43	0.038
	Missing	74	43/236					

PY: Person-Years
* 3 patients with date of CHD missing were not included in survival analyses;
** Fold change upper reference limit;
□ Median value

Fig. 1 Overall survival (N=133 *) after diagnosis of CHD. Median FU (Q1-Q3) in years: 1.4 (0.7-4.0)



Deaths	Median OS (95% CI)	1-y OS (95% CI)	2-y OS (95% CI)	3-y OS (95% CI)	4-y OS (95% CI)	5-y OS (95% CI)	6-y OS (95% CI)
88/133 (66.2%)	2.4 (1.6-2.9)	72.5 (63.7-79.5)	53.1 (43.7-61.7)	40.5 (31.4-49.5)	34.5 (25.7-43.4)	29.1 (20.7-38.0)	24.0 (16.0-32.8)

The evaluation of 1/23 patients (4%) has been considered too early

Conclusion: This is the first study of CHD capturing clinical data over the last decade and suggesting the potential role of some relevant prognostic markers in the management of CHD. Our data can be used to design future prospective studies.