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Carcinoid Heart Disease: Prognostic Value of 5-Hydroxyindoleacetic Acid Levels and Impact on Survival: A Systematic Literature Review

Amy Buchanan-Hughes[a] Alex Pashley[a] Marion Feuilly[b] Florence Marteau[b]
D. Mark Pritchard[c] Simron Singh[d]

[a]Costello Medical, Cambridge, UK; [b]Ipsen Pharma, Boulogne-Billancourt, France; [c]University of Liverpool, Liverpool, UK; [d]University of Toronto, Toronto, ON, Canada

Keywords
Carcinoid syndrome · Carcinoid heart disease · Neuroendocrine tumours

Abstract
Background: Carcinoid heart disease (CHD) can develop in patients with carcinoid syndrome (CS), itself caused by overproduction of hormones and other products from some neuroendocrine tumours. The most common hormone is serotonin, detected as high 5-hydroxyindoleacetic acid (5-HIAA). This systematic literature review summarises current literature on the impact of CHD on survival, and the relationship between 5-HIAA levels and CHD development, progression, and mortality. ***Methods:*** MEDLINE, Embase, Cochrane databases, and grey literature were searched using terms for CHD, 5-HIAA, disease progression, and mortality/survival. Eligible articles were non-interventional and included patients with CS and predefined CHD and 5-HIAA outcomes. ***Results:*** Publications reporting on 31 studies were included. The number and disease states of patients varied between studies. Estimates of CHD prevalence and incidence among patients with a diagnosis/symptoms indicative of CS were 3–65% and 3–42%, respectively. Most studies evaluating survival found significantly higher mortality rates among patients with versus without CHD. Patients with CHD reportedly had higher 5-HIAA levels; median urinary levels in patients with versus without CHD were 266–1,381 versus 67.5–575 μmol/24 h. Higher 5-HIAA levels were also found to correlate with disease progression (median progression/worsening-associated levels: 791–2,247 μmol/24 h) and increased odds of death (7% with every 100 nmol/L increase). ***Conclusions:*** Despite the heterogeneity of studies, the data indicate that CHD reduces survival, and higher 5-HIAA levels are associated with CHD development, disease progression, and increased risk of mortality; 5-HIAA levels should be carefully managed in these patients.

Introduction

Carcinoid syndrome (CS) refers to a spectrum of symptoms caused by excessive production of hormones and other tumour products from some neuroendocrine tumours (NETs) [1]. The incidence of NETs in the United States (US) was estimated to be 6.98 per 100,000 in 2012, with an approximate annual prevalence of 0.048% [2]. A subset of patients with NETs (approximately 20%) develop CS [3]. The secreted tumour products responsi-

karger@karger.com
www.karger.com/nen

Amy Buchanan-Hughes
Costello Medical
50/60 Station Road
Cambridge, CB1 2JH (UK)
Amy.Buchanan-Hughes@costellomedical.com

Table 1. Eligibility criteria for the SLR

PICOS domain	Inclusion criteria	Exclusion criteria
Patient population	Adults with CS	– Adults without CS – Children (<18 years old) with CS – Populations where outcomes are not presented separately for the patients of interest
Intervention(s)	Any or none	–
Comparator(s)	Any or none	–
Outcomes	– Number of patients with and without CHD – Number of patients who died from CHD, and the mean survival in patients with and without CHD – Baseline 5-HIAA level in patients with and without CHD, and in patients who died from CHD – Increase in 5-HIAA level associated with disease progression – Risk of disease progression associated with 5-HIAA level – Risk of CHD death associated with 5-HIAA level	Studies not presenting relevant outcomes for the population of interest
Study designs	– Observational studies: – Analytical (longitudinal cohort or case-control studies, cross-sectional studies) – Descriptive (surveillance and surveys, ecological studies) SLRs and meta-analyses of relevant primary publications were included at the title/abstract screening stage and used for the identification of any additional primary studies not identified through the database searches but were subsequently excluded at the full-text screening stage	– Any other study design, including: – Narrative reviews – Editorials, notes, comments or letters – Case reports/case studies – Economic evaluations – RCTs/interventional non-RCTs
Other considerations	– Abstract or full text in English – Human participants – Conference abstracts from 2016 onwards	– Abstract or full text not in English – Non-human participants – Conference abstracts from prior to 2016

5-HIAA, 5-hydroxyindoleacetic acid; CHD, carcinoid heart disease; CS, carcinoid syndrome; PICOS, patients, interventions, comparators, outcomes and settings; RCT, randomised controlled trial; SLR, systematic literature review.

ble for disease development (serotonin being the most prominent) are ordinarily degraded by the liver [4, 5]. However, CS is often associated with liver metastases, allowing unmetabolised NET secretions to circulate at higher levels, leading to disease development and progression [5, 6].

Elevated serotonin levels cause a range of symptoms including cutaneous flushing, diarrhoea, and bronchoconstriction [6], experienced by 90%, 80% and 15% of patients with CS, respectively [7, 8]. In addition to these symptoms, it has been reported that approximately half of individuals with CS will develop carcinoid heart disease (CHD), a potentially life-threatening complication [6, 9]. Although the exact pathophysiology of CHD is not well understood, the secretion of hormones and other products from tumours is suspected to lead to the deposition of cardiac plaques, which are primarily found on the right side of the heart (~90% of cases) [1, 10]. There is currently a lack of consensus regarding the diagnosis, management, and preventative measures for CHD, despite patients having significantly worse life expectancy than those with CS alone [1, 6].

The principal laboratory test to analyse serotonin overproduction in individuals with CS is the measurement of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, in urine or plasma [4, 5]. The aim of this systematic literature review (SLR) was to summarise the published quantitative evidence on the association between high urine and/or plasma 5-HIAA concentration and CHD development, and the impact of CHD on survival.

Methods

Search Strategy

A systematic search of MEDLINE, Embase, Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Reviews of Effect (DARE) was conducted on the 4th May 2018, using

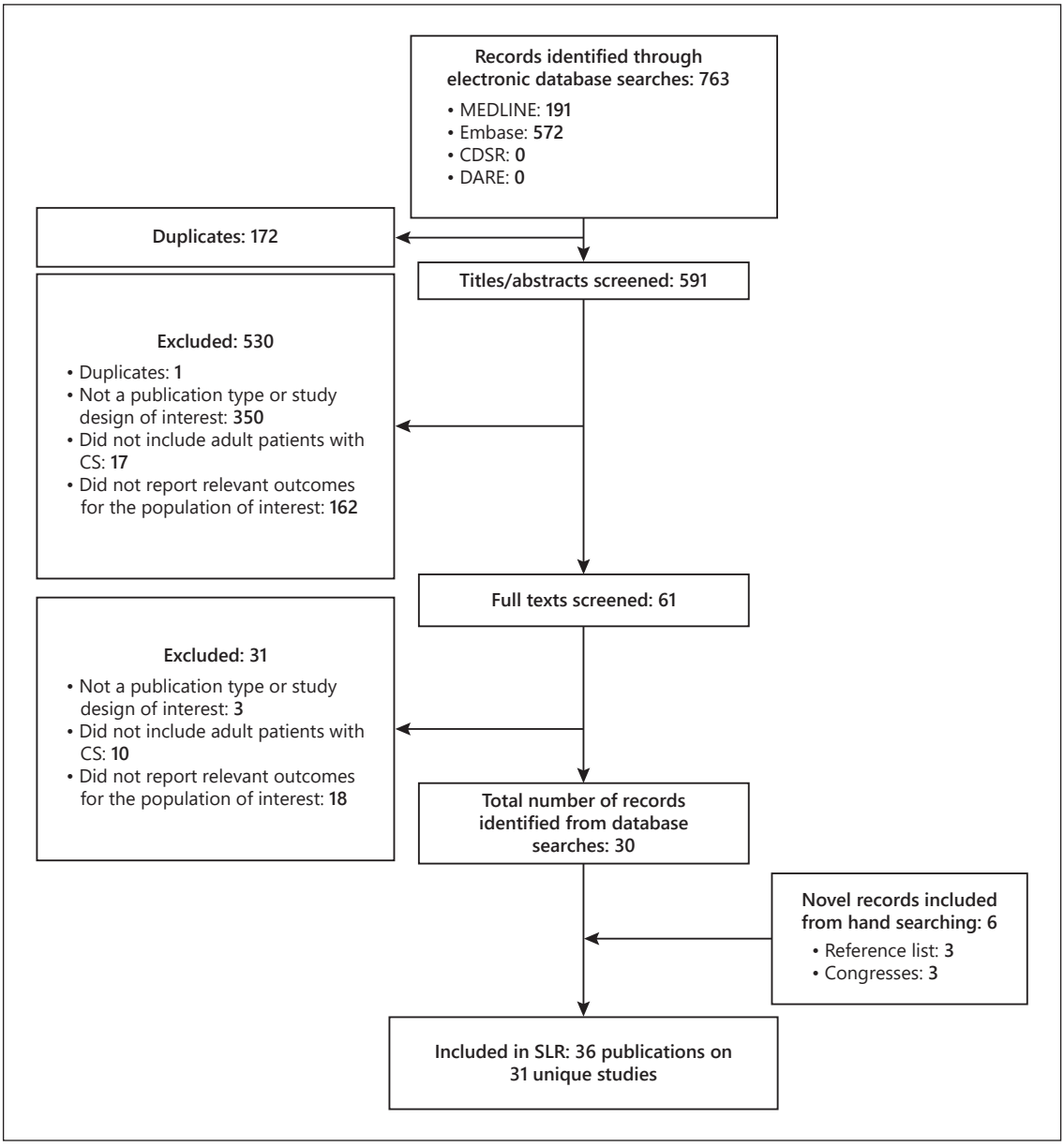

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. CDSR, Cochrane Database of Systematic Reviews; CS, carcinoid syndrome; DARE, Database of Abstracts of Reviews of Effects; SLR, systematic literature review.

predefined search terms for CHD, 5-HIAA, disease progression, mortality, and survival. Supplementary searches of article reference lists and congress abstracts from oncology and neuroendocrine-specific congresses were also carried out to ensure that no relevant studies were missed. Conference abstracts from prior to 2016 and any studies not published in English were excluded. Full details of the searches are provided in the supplementary information (online suppl. Tables S1–S4; for all online suppl. material, see www.karger.com/doi/10.1159/000506744). The SLR was conducted in line with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the University of York Centre for Reviews and Dissemination's (CRD) Guidance for Undertaking Reviews in Health Care [11, 12].

Eligible articles had to describe observational studies that included patients with CS and reported data on predefined CHD outcomes. An overview of the patients, interventions, comparators, outcomes, and study designs used for the SLR is shown in Table 1.

Table 2. Study characteristics of the included articles

First author [Ref.], year	Country	Study period	Duration of follow-up	Study population
Ardill [38], 2016	UK	NR	2 years	20 patients who died from SB-NETs
Bergestuen [35], 2009	Norway	1983–2007	Range 0.3–24.3 years	258 patients with SI-NETs
Bernheim [49], 2008	US	1980–2005	NR	265 patients with CHD
Bhattacharyya [22], 2011	UK	2006–2010	Median 29 (IQR 24–36) months	252 patients with histologically proven metastatic carcinoid tumours of midgut origin and CS
Connolly [47], 1995	US	NR	Mean 28 months (range 4 months–5.2 years)	26 patients with symptomatic CHD who underwent valvular surgery
D'Arienzo [24], 2017	UK	1998–2017	Median 45.7 months	139 patients with CS
Davis [14], 1973	US	NR	NR	94 patients with malignant CS
Denney [17], 1998	US	1986–1991	NR	23 patients with CS
Dobson [23], 2014	UK	2009–2013	Median 27 (IQR 12–37) months; total of 2,862 patient years	137 patients with non-pancreatic NETs, liver metastases and/or CS
Fijalkowski [26], 2018	Germany	2002–2016	NR	182 patients with CS
Himelman [15], 1989	US	1972–1987	Mean 8.1 (SD 6.9)	30 patients with CS
Hoffmann [18], 2001	Germany	1997	Mean 18 (SD 7) months	35 patients with known CS, suffering from metastatic carcinoid tumours
Janson [29], 1997	Sweden	1978–1993	NR	301 carcinoid patients (256 midgut, 39 foregut and 6 hindgut)
Kinney [30], 2001	US	1983–1996	NR	119 patients who underwent abdominal surgery for metastatic carcinoid tumours
Korach [46], 2016	Israel, US	2008–2013	Mean 24.4 (SD 21, range 4–84) months	17 patients undergoing valve operations for CHD
Makridis [44], 1997	Sweden	1980–1993	Mean 6.9 (range 3–13) years	121 patients with midgut carcinoid tumours
Mansencal [21], 2010	France	1998–2007	Mean 26 (range 12–82) months	80 patients with histologically proven digestive endocrine tumours and CS
Meijer [19], 2002	The Netherlands	1996–1998	NR	20 patients with a histologically proven midgut carcinoid tumours leading to CS
Møller [20], 2003	US	1980–2001	≤25% change in echocardiogram: mean 1.9 (range 1.3–3.1) years >25% change: mean 2.3 (range 1.2–3.2) years	103 patients with histologically verified carcinoid tumours and CS
Møller [45], 2005	US	1981–2000	NR	200 patients with CS referred for echocardiography, in whom the diagnosis of CHD was confirmed
Norlén [36], 2012 (Subgroup: Norlén [37], 2013)	Sweden	1985–2012	Mean 6.9 (SD 5.2) years (median 12 [range 0–27] years)	603 patients with histopathologically verified SI-NETs (394 patients with SI-NETs who had their primary tumour resected and had liver metastases)
Nykjær [33], 2007	Denmark	1994–2003	NR	56 patients with histopathologically verified midgut carcinoid tumours
Pellikka [16], 1993	US	1980–1989	NR	132 patients with carcinoid syndrome who underwent echocardiographic study
Riechelmann [27], 2018 Mesquita [25], 2017	Argentina, Brazil	2009–2017	NR	65 patients (42 recruited in Brazil; 23 recruited in Argentina) with advanced NETs and CS and/or elevated u5-HIAA, who underwent screening echocardiograms for CHD
Robiolio [28], 1995	NR	1972–1994	NR	604 patients with carcinoid tumours

Table 2 (continued)

First author [Ref.], year	Country	Study period	Duration of follow-up	Study population
Rodríguez Laval [39], 2018	Germany	2008–2014	MF not present: median 47 (range 31–78) months MF present: median 51 (range 28–75) months	81 patients with pathologically proven NETs with the primary site in the midgut and mesenteric lymphatic metastases on imaging
Toumpanakis [41–43], 2016	UK	NR	NR	600 patients with advanced SB-NETs[a]
van der Horst-Schrivers [34], 2007	The Netherlands	1992–2003	Median 55 (range 0.5–143) months	76 patients with disseminated midgut carcinoid tumours
Weingarten [48], 2007	US	1985–2003	NR	100 patients with symptomatic CHD who underwent surgery
Westberg [40], 2001	Sweden	1985–1998	Mean 85 (SEM 8) months	64 patients with midgut CS
Zuetenhorst [31], 2003 Zuetenhorst [32], 2004	The Netherlands	1999–2000	NR	37 carcinoid patients (2003); 32 patients with NETs (2004)

CHD, carcinoid heart disease; CS, carcinoid syndrome; IQR, interquartile range; MF, mesenteric fibrosis; NET, neuroendocrine tumour; NR, not reported; SD, standard deviation; SEM, standard error of the mean; SB-NET, small bowel neuroendocrine tumour; SI-NET, small intestinal neuroendocrine tumour; u5-HIAA, urinary 5-hydroxyindoleacetic acid. [a] The most recent conference abstract listed 600 patients, whereas the two previous abstracts indicated only 572 patients were analysed; the outcomes reported were identical, so the more recent figure was used.

Article Screening and Data Extraction

Titles and abstracts of all potentially relevant publications were screened against the predefined eligibility criteria by two independent reviewers. For references that were considered potentially relevant, the full publication was retrieved, and its relevance was assessed against the eligibility criteria by two independent reviewers. At both stages, in the event of disagreement, a third reviewer was consulted to make the final decision. Publications suitable for inclusion were extracted into a predefined extraction grid by one reviewer and checked for accuracy and completeness by a second reviewer. The quality of study reporting was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [13].

Results

Characteristics of the Captured Studies

From the 591 unique citations identified by the database searches, 30 publications reporting 29 studies were included in the SLR, with a further 6 unique publications identified from additional hand searches. Therefore, a total of 36 publications representing 31 studies were included for extraction (Fig. 1). An overview of the study characteristics of the extracted articles is given in Table 2.

The number of included patients varied widely between studies, from 17 to 604, and a range of disease states were reported on, including small bowel NETs and non-pancreatic NETs with liver metastases. The study period (reported in 27 studies) ranged from 1 to 27 years. The majority of studies (18) were conducted in Europe, 11 were conducted in the US (one of which was also conducted in Israel), one was conducted in South America, and one did not report a geographical location (Table 2). Data on patient ethnicity were not collected in this SLR.

Prevalence and Incidence of CHD

A total of 24 studies reported details on the prevalence or incidence of CHD within their patient populations: 23 studies reported the number of patients with CHD at baseline, and 7 studies reported the development of CHD in patients over their designated study period (Fig. 2). Fourteen of the 24 studies explicitly stated that their patients had CS [14–27]; 10 studies described patients with NETs including gastrointestinal NETs, or described symptoms typical of CS (such as diarrhoea or flushing), but did not specifically report CS [28–39].

The percentage of patients with CHD at baseline ranged from 3% to 65% [20, 28]. The percentage of patients with CS who developed CHD ranged from 3% to 22% [17, 23, 36, 37], affording crude calculated incidence values ranging from 3% to 42% among patients who did not have CHD at baseline [20, 36, 37]; however, variation in the lengths of these studies prevented comparison and any meaningful conclusions from being drawn (Fig. 2). Several studies featured patients who were referred for echocardiography based on suspicion of CHD, implying potential selection bias [16, 20, 25, 27]. Removing these

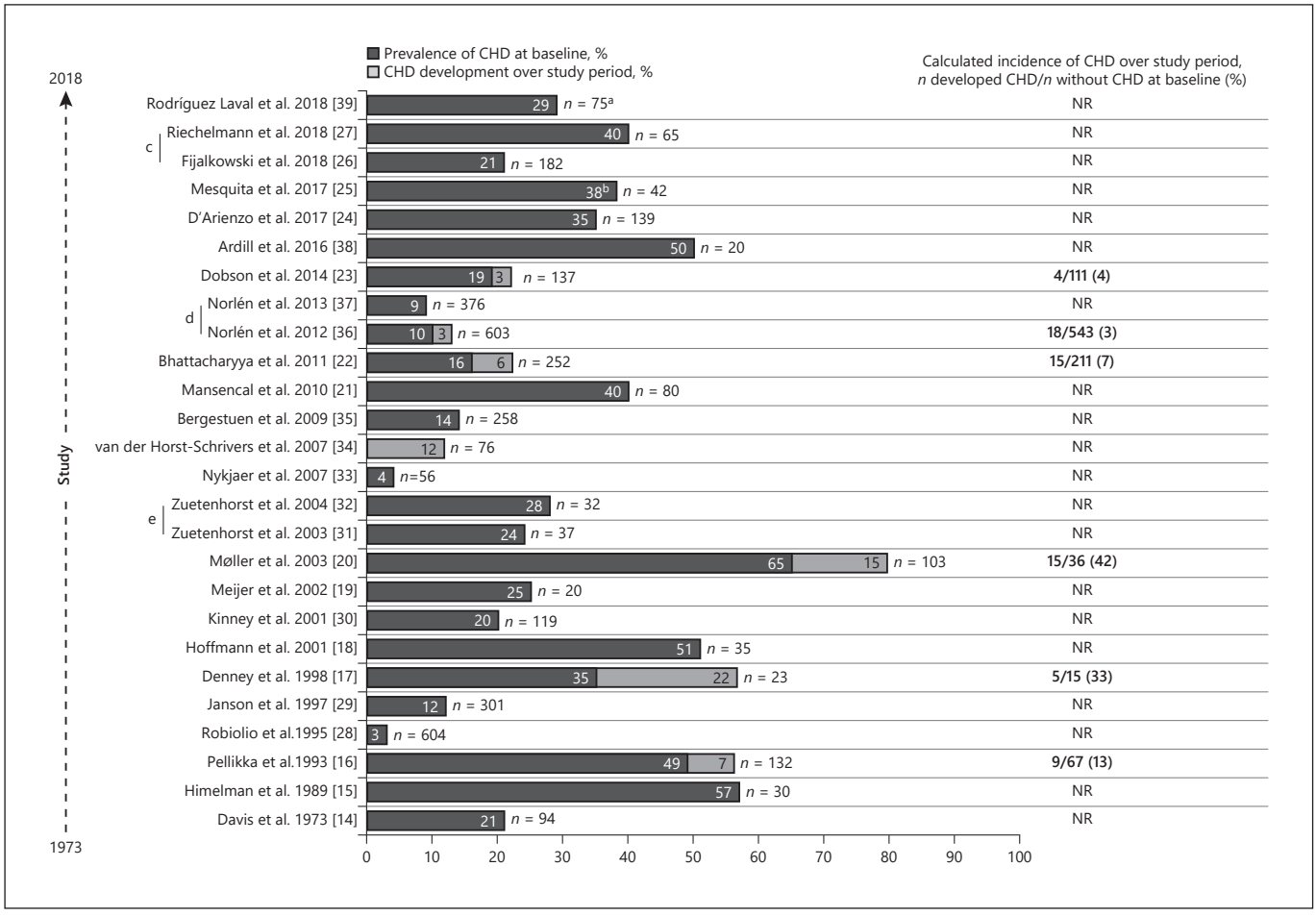

Fig. 2. Prevalence and incidence of carcinoid heart disease (CHD). [a] $n = 81$, 6 cases missing; [b] 45% (19 patients) when CHD is defined as at least mild valve regurgitation. [c–e] Different publications on the same study. NR, not reported.

studies would decrease the highest reported CHD prevalence estimates from 65% to 57% [15], and the highest calculated crude incidence figures from 42% to 33% [17].

Survival in Patients with and without CHD

Fourteen studies reported the survival of patients with CHD, 11 of which also reported survival in patients without CHD (Table 3) [15–18, 23, 28, 29, 31, 32, 35–37, 40–43]. Survival was found to be lower in patients with CHD versus patients without CHD in all studies that reported both, with the comparison reaching statistical significance in 8 studies [15, 16, 18, 23, 31, 32, 36, 37, 41–43]. Two studies reported a non-significant result [29, 35]; the remaining studies did not analyse these outcomes for significance, or used descriptive statistics only [17, 28, 40, 44–46].

Four studies evaluated survival or mortality at specified timepoints for patients with and without CHD [16, 17, 35, 40]. Pellikka et al. [16] reported that 3-year survival for patients with CHD was 31%, compared with 68% for patients with no echocardiographic evidence of cardiac involvement ($p = 0.0003$). Similarly, Bergestuen et al. [35] reported 50% 5-year survival for patients with CHD, compared with 76% for those without ($p = 0.02$ [univariate analysis]; $p = 0.25$ [multivariate analysis]). Westberg et al. [40] and Denney et al. [17], who reported outcomes at 5 and 6 years, respectively, found worse survival among patients with CS and CHD than those without CHD. They also reported worse survival in patients with relatively severe CHD disease, though it is not clear whether the results of these subgroup comparisons were statistically significant [17, 40]. Additionally, Korach et al. [46],

Table 3. Survival in patients with and without CHD

First author [Ref.], year	Median (95% CI) survival, years			Absolute survival, *n/N* (%, 95% CI)		Additional comments
	with CHD	without CHD	time point, years	with CHD	without CHD	
Bergestuen [35], 2009	5.3 (3.6–7.1) Univariate HR: 1.76 (1.09–2.84) Multivariate HR: 0.70 (0.38–1.29)	9.3 (7.2–11.5)	5	NR (50)	NR (76)	Univariate analysis: $p = 0.02$ Multivariate analysis: $p = 0.25$
Bernheim [49], 2008	NR	NR	5	Patients who had hepatic resection performed during follow-up: NR (86.5, 73.5–100) Patients without hepatic resection: NR (29.0, 23.3–36.1)	NR	Survival after diagnosis; survival curve available for hepatic resection vs. no hepatic resection
Denney [17], 1998	NR	NR	6	Developed new CHD: 3/5 (60%) CHD, no progression: 1/7 (14%) CHD progression: 1/1 (100%)	3/10 (30)	p = NR
Dobson [23], 2014	6.5 (0.1 – not reached)[a, b] HR: 3.61 (1.69–7.69)	20.2 (1.0 – not reached)[a, b]	NR	NR	NR	Kaplan-Meier survival curve available; $p = 0.001$ for univariate analysis
Himelman [15], 1989	Mean 1.9 (SD 1.4)	Mean 3.8 (SD 2.9)	NR	NR	NR	Survival after the first echocardiogram; $p = 0.05$
Hoffmann [18], 2001	11 months (5 months – not reached)[a, b]	Not reached (9 months – not reached)[a, b]	NR	NR	NR	Kaplan-Meier survival curve available; $p = 0.04$
Janson [29], 1997	46 months	94 months	NR	NR	NR	Midgut carcinoid patients with/without CHD (NS, $p = 0.09$)
Korach [46], 2016	27 (1–81) months[a]	NR	4	Mean 23% (SD 14%)	NR	Actuarial survival after valve replacement for CHD; Kaplan-Meier survival curve available; p = NR
Makridis [44], 1997	5.0 (NR)	NR	NR	NR	NR	90% CIs were determined using patients with no CS, rather than no CHD, and as such have not been presented here; p = NR
Møller [45], 2005	2.6 (1.6–3.2)	NR	NR	NR	NR	Median survival from first diagnosis of metastatic carcinoid disease was 5.9 (95% CI 5.0–6.8) years; p = NR
Norlén [36, 37], 2012	HR: 2.52 (1.76–3.61)		NR	NR	NR	Overall survival; $p < 0.001$
Pellikka [16], 1993	1.6	4.6	3	NR (31)	NR (68) for those without echocardiographic evidence of cardiac involvement	$p = 0.0003$
Robiolio [28], 1995	4.8 (3.8–13.3)	7 (5.0–9.2)	NR	NR	NR	Survival is from time of diagnosis; p = NR
Toumpanakis [41–43], 2016	HR: 5 (NR), SE: 2.26		3 5	NR (38) NR (25)	NR	$p < 0.001$
Westberg [40], 2001	Severe CHD: 54 (6–95) months[a] Moderate CHD: not reached (9 months – not reached)[a, b] Mild CHD: not reached (8 months – not reached)[a, b]	Not reached (12 months – not reached)[a,b]	5	Severe CHD: 30% Moderate CHD: 70% Mild CHD: 70%	75%	Kaplan-Meier survival curve available; p = NR
Zuetenhorst [31, 32], 2003	13 months (5 months – not reached)[a, b]	Not reached (6 months – not reached)[a, b]	NR	NR	NR	Kaplan-Meier survival curve available; $p = 0.026$

[a] Value determined from Kaplan-Meier survival curve by digitisation: three readings were taken and the mean of these values was used; [b] Value not reached according to the Kaplan-Meier survival curve due to insufficient follow-up period. CHD, carcinoid heart disease; CI, confidence interval; CS, carcinoid syndrome; HR, hazard ratio; NR, not reported; NS, not significant; SD, standard deviation; SE, standard error.

who recruited patients with CHD exclusively, reported 4-year survival of 23% after valve replacement.

Four studies reported univariate or multivariate analyses of mortality risk in patients with CS and CHD versus CS without CHD (Fig. 3) [23, 35–37, 41–43]. Through a univariate analysis, Dobson et al. [23] showed that the risk of death was significantly greater in patients with CHD at baseline, compared with those without CHD (hazard ratio [HR]: 3.61; 95% confidence interval [CI]: 1.69–7.69; $p = 0.001$). This study also found that a five-point increase in echocardiographic score resulted in an odds ratio (OR) of 2.66 for death (95% CI: 1.63–4.35; $p <$

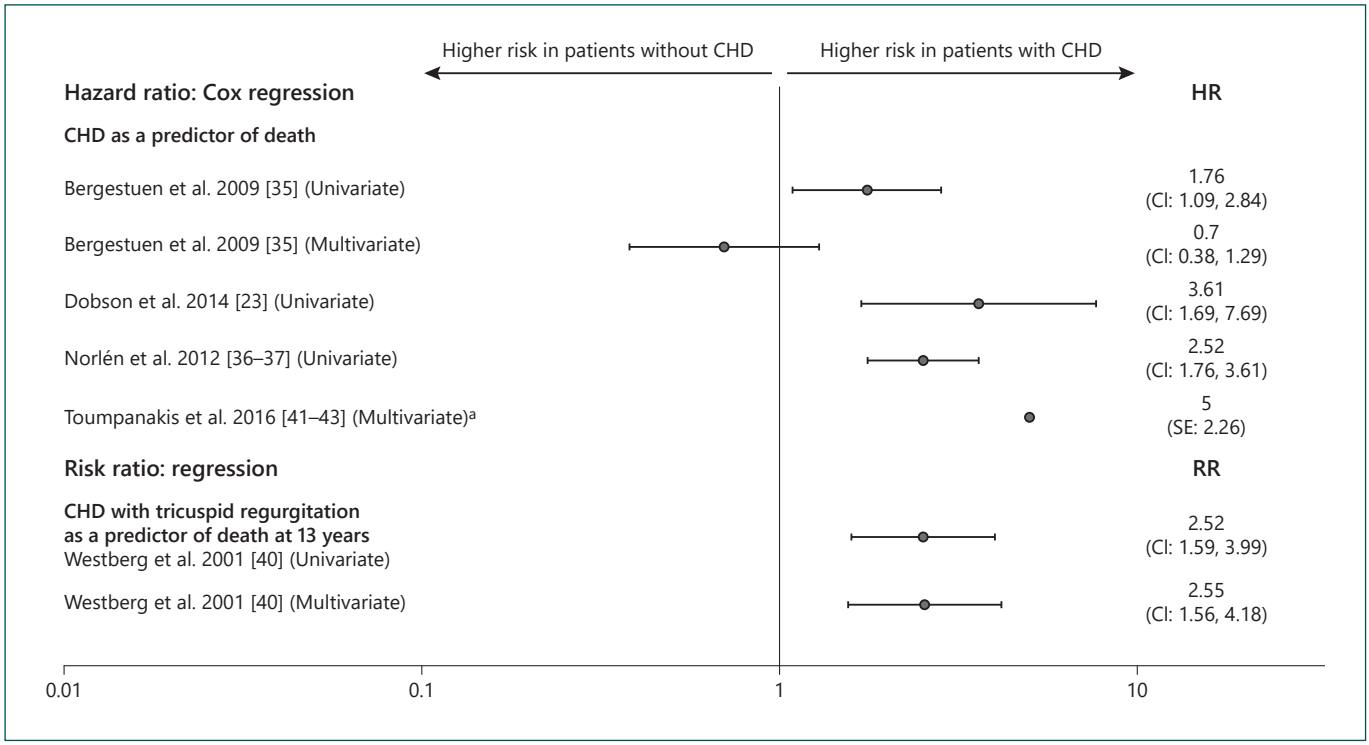

Fig. 3. Carcinoid heart disease (CHD) as a predictor of death. [a] Confidence intervals were not reported in this publication. The published SE value was used to estimate the 95% confidence interval (CI) using the methods described in Hackshaw [54]. A 95% CI of 0.06–419.49 was obtained, corresponding to a statistically insignificant result, in contrast to the published *p* value (<0.001). This study has been published in the form of conference abstracts only and no further information on the statistical methods is available. HR, hazard ratio; RR, risk ratio.

0.005) [23]. Bergestuen et al. [35] employed both types of analysis in patients with small intestinal NETs and CS, finding that CHD was a significant predictor of death in univariate analyses (HR: 1.76; 95% CI: 1.09–2.84; $p = 0.02$), but not in the multivariate analysis (HR: 0.70; 95% CI: 0.38–1.29; $p = 0.25$). Only distant metastases, the NET marker chromogranin A ≥6.2 × the upper limit of its normal concentration, and age ≥64 years were significant predictors of death in the multivariate analysis [35].

Two of the 4 studies used multivariate analyses exclusively [36, 37, 41–43]. In Norlén et al. [36, 37], CHD was associated with an HR of 2.52 (95% CI: 1.76–3.61; $p < 0.001$) for overall survival (vs. patients without CHD). In Toumpanakis et al. [41–43], the presence of severe CHD (definition not provided) was reported to have a significant impact on overall survival versus the absence of CHD, with an HR of 5.00 (standard error [SE]: 2.26; $p < 0.001$) when adjusting for tumour grade, metastases, and age. However, calculation of a 95% CI using the reported SE value suggests an insignificant result (Fig. 3).

In a study that used echocardiographic examination to predict the prognosis of patients with CS, Westberg et al. [40] evaluated the impact of eight variables on survival using univariate analyses. The study found that the only variables to significantly increase the relative risk of death were older age at diagnosis, tricuspid regurgitation (TR), and tricuspid structural abnormalities (TSA) + TR; a TSA + TR score of one or more was considered pathological. Their multivariate analysis also showed an increased risk of death in patients with TR (Fig. 3).

Association between 5-HIAA Levels and CHD Diagnosis, Progression, and Mortality

A total of 19 studies reported baseline levels of urinary 5-HIAA (u5-HIAA) in patients with CHD [15–21, 25, 27–29, 31, 32, 34, 35, 40, 45–49]; of these, 13 studies also presented baseline levels of u5-HIAA in patients without CHD (Table 4) [15–18, 20, 21, 25, 27–29, 31, 32, 34, 35, 40].

Table 4. Urinary 5-HIAA levels in CHD patients

First author [Ref.], year	u5-HIAA units of measurement	Baseline u5-HIAA levels in patients with CHD	Baseline u5-HIAA level in patients without CHD	*p* value (CHD vs. non-CHD)
Bergestuen [35], 2009	μmol/24 h	Median 783 (range 9–2,160)	Median 67.5 (range 0–1,980)	<0.001
Bernheim [49], 2008	mg/24 h	Median 183 (IQR 83–300)	NR	–
Connolly [47], 1995	mg/24 h	Median 172 (range 2.1–416)	NR	–
Denney [17], 1998	mg/24 h	Median 144.6 (range 99–358); initially had CHD Median 319 (range 193–356); developed CHD	Median 106.7 (range 59–193); initially no CHD Median 77 (range 42–112); no CHD, no development	NS
Himelman [15], 1989	mg/24 h	Maximum level: mean 331 (SD 231) Mean level: mean 203 (SD 105)	Maximum level: mean 58 (SD 78) Mean level: mean 47 (SD 75)	Maximum level: <0.001 Mean level: <0.001
Hoffmann [18], 2001	μmol/24 h	Mean 713 (SD 669)	Mean 175 (SD 305)	0.005
Janson [29], 1997	μmol/24 h	Mean 814	Mean: 441	<0.001
Korach [46], 2016	mg/24 h	Mean 61 (SD 36)	NR	–
Mansencal [21], 2010	mg/24 h	Mean 384 (SD 431)	Mean 43 (SD 25)	<0.0001
Meijer 2002 [19],	μmol/mol creatinine	Median 16.5 (range 6.7–200.1)	NR	–
Møller [20], 2003	mg/24 h	Median 209 (IQR 79–306)	Median 110 (IQR 49–177)	0.02
Møller [45], 2005	mg/24 h	Median 264 (range 187–391)	NR	–
Pellikka [16], 1993	mg/24 h	Mean 270 (SD 154)	Mean 131 (SD 149)	<0.001
Riechelmann [25, 27], 2018	mg/24 h (assumed; reported as "mg" only in publication)	Median 50.8	Median 25.4	NS
Robiolio [28], 1995	mg/24 h	Mean 219 (SD 124)	Mean 55.3 (SD 141)	<0.0001
van der Horst-Schrivers [34], 2007	mmol/mol creatinine	Median 52.8 (range 8.5–252.0)	Median 18.6 (range 1.3–418.4)	0.085
Weingarten [48], 2007	mg/24 h	1985–1994: median 206 (10%, 90% quantiles 12–315) 1995–2003: median 128 (10%, 90% quantiles 31–362)	NR	–
Westberg [40], 2001	μmol/24 h	Mean 635 (SEM 91)	Mean 306 (SEM 105)	NR
Zuetenhorst [31], 2003 Zuetenhorst [32], 2004	μmol/24 h	2003: median 576 (range 87–1,028) 2004: median 815 (range 87–1,185)	2003: Median 233 (range 17–1,616) 2004: Median 206 (range 19–1,116)	2003: 0.02 2004: 0.007

CHD, carcinoid heart disease; IQR, interquartile range; NR, not reported; NS, not significant; SD, standard deviation; SEM, standard error of the mean; u5-HIAA, urinary 5-hydroxyindoleacetic acid.

In the majority of studies, patients with CHD were found to have mean and median u5-HIAA levels that were greater than double those found in patients without CHD (Fig. 4; variability within individual studies is shown in Table 4). Following conversion to μmol/24 h for studies using mg/24 h, the mean and median baseline levels of u5-HIAA in patients with versus without CHD were 319–2,009 versus 175–685 μmol/24 h, and 266–1,381 versus 67.5–575 μmol/24 h, respectively [15–18, 20, 21, 25, 27–29, 31, 32, 35, 40, 45–49]. Two studies presented their u5-HIAA measurements in mmol or μmol per mole of creatinine and, as such, could not be directly compared [19, 34].

Six studies reported the association of 5-HIAA levels with the progression of CHD [17, 20–23, 39, 40]. Higher u5-HIAA levels (plasma levels in Dobson et al. [23]) were generally associated with disease progression in these studies. The median 5-HIAA level associated with disease progression and/or worsening ranged from 791 to 2,247 μmol/24 h [17, 20, 22]; Westberg et al. [40] presented mean values according to mild, moderate or severe disease, ranging from 408 to 901 μmol/24 h (Table 5).

Seven studies performed univariate or multivariate analyses to investigate the association of 5-HIAA levels with CHD development/progression (Table 5) [17, 20–23, 39]. Rodríguez Laval et al. [39] observed, in both their univariate and multivariate analyses, that u5-HIAA levels >501 μmol/24 h were a significant risk factor for the development of CHD. Through a multivariate Poisson regression analysis, Bhattacharyya et al. [22] found that the risk of CHD progression in patients with u5-HIAA levels of 300–599, 600–899, and ≥900 μmol/24 h was 2.74, 3.16, and 3.40 times higher, respectively, than in patients with u5-HIAA levels <300 μmol/24 h. A multivariate logistic regression model by Møller et al. [20] showed that, in patients with CHD, peak u5-HIAA level was a significant predictor of a >25% change in cardiac score (considered suggestive of disease progression; OR: 1.08 for each in-

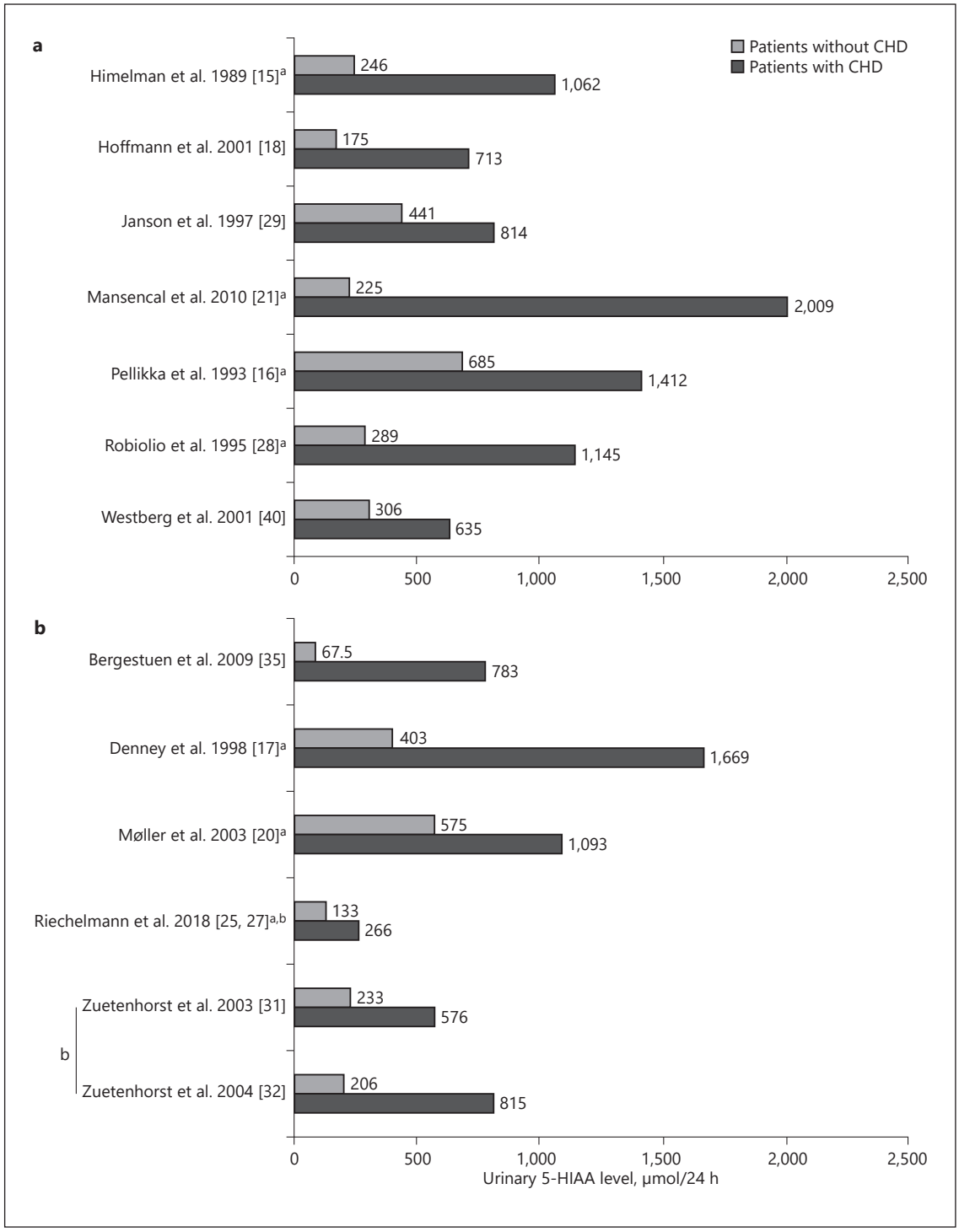

Fig. 4. Mean (**a**) and median (**b**) urinary 5-hydroxyindoleacetic acid (5-HIAA) levels in patients with or without carcinoid heart disease (CHD). [a] Levels reported in mg/24 h converted to μmol/24 h for purposes of comparison. [b] Different publications on the same study.

Table 5. 5-HIAA levels and CHD progression

First author [Ref.], year	5-HIAA units of measurement in urine or plasma	5-HIAA level associated with disease progression
Bhattacharyya [22], 2011	μmol/24 h (urine)	5-HIAA level at time of progression: median 791 (IQR 581–1,084.5) 5-HIAA level in previous 6 months for this group: median 460.5 (IQR 309–948.5); $p = 0.001$
Denney [17], 1998	mg/24 h (urine)	Patients with CHD progression or development at baseline: median 256 (range 145–356) Reference group: median 98.8 (range 59–186); $p < 0.005$
Dobson [23], 2014	nmol/L (plasma)	CHD progression: median 2,247 (range 807–2,939) No CHD progression: median 316 (138–661) Died prior to second echocardiogram: median 1,221 (range 167–437); $p = 0.009$
Mansencal [21], 2010	mg/24 h (urine)	Baseline: With CHD: mean 384 (SD 431); without CHD: mean 43 (SD 25); $p < 0.0001$ At follow-up (mean duration 26 months): Correlation between u5-HIAA and right-sided CHD score: $r = 0.75$; $p < 0.0001$; left-sided CHD score: $r = 0.83$, $p < 0.001$; overall CHD score: $r = 0.84$; $p < 0.0001$
Møller [20], 2003	mg/24 h (urine)	Baseline: Progressors: median 166 (IQR 86–303); reference group: median 115 (IQR 49–212); $p = 0.005$ Highest value: progressors: median 265 (IQR 209–593); reference group: median 189 (IQR 75–286); $p = 0.004$
Rodríguez Laval [39], 2018	μmol/24 h (urine)	5-HIAA ≥501 μmol/24 h as a risk factor for CHD development Univariate analysis: OR 17.6 (95% CI 4.9–62.8); $p < 0.001$ Multivariate analysis: HR 14.7 (95% CI 3.8–55.3); $p < 0.001$
Westberg [40], 2001	μmol/24 h (urine)	Reference: mean 306 (SEM 105) Mild CHD: mean 556 (SEM 163) Moderate: mean 408 (SEM 86) Severe: mean 901 (SEM 196) p = NR

5-HIAA, 5-hydroxyindoleacetic acid; CHD, carcinoid heart disease; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NR, not reported; OR, odds ratio; SD, standard deviation; SEM, standard error of the mean.

crease of 25 mg/24 h; 95% CI: 1.03–1.13; $p = 0.009$). Denney et al. [17] reported that mean post-treatment u5-HIAA level was a significant predictor of CHD progression in a multiple stepwise regression analysis ($p < 0.005$). In a linear regression analysis, Mansencal et al. [21] identified a strong correlation between u5-HIAA levels and CHD severity as scored out of 30, accounting for right- and left-sided CHD (scored out of 20 and 10, respectively). Through a univariate analysis, Dobson et al. [23] found that every 100 nmol/L increase in plasma 5-HIAA was associated with a 5% increase in the odds of CHD progression before a patient's second follow-up (within a median follow-up period of 27 months; OR: 1.05; 95% CI: 1.01–1.09; $p = 0.012$).

Two studies presented data regarding the association of 5-HIAA levels with CHD mortality (Table 6) [23, 48]. Dobson et al. [23] found that every 100 nmol/L increase in plasma 5-HIAA was associated with a 7% increase in the odds of death before second follow-up (OR: 1.07; 95% CI: 1.03–1.10; $p = 0.001$). In a study on patients with CHD, Weingarten et al. [48] found that patients with higher u5-HIAA levels had higher mortality rates compared with patients with lower u5-HIAA levels, although the association was not statistically significant (logistic regression,

Table 6. 5-HIAA levels associated with CHD mortality

First author [Ref.], year	5-HIAA units of measurement in urine or plasma	5-HIAA level and mortality in CHD patients
Dobson [23], 2014	nmol/L (plasma)	Baseline 5-HIAA concentration was significantly associated with disease progression: every 100 nmol/L increase in 5-HIAA yielded 7% higher odds of death before second follow-up (OR 1.07, 95% CI: 1.03–1.10; $p = 0.001$)
Weingarten [48], 2007	mg/24 h (urine)	Deaths: 0–6 mg/24 h: 0/2 (0%) 7–100 mg/24 h: 2/27 (7%) 101–200 mg/24 h: 3/25 (12%) 201–300 mg/24 h: 6/23 (26%) >300 mg/24 h: 2/12 (17%) Adjusted $p = 0.28$ (NS)

5-HIAA, 5-hydroxyindoleacetic acid; CHD, carcinoid heart disease; CI, confidence interval; NS, not significant; OR, odds ratio.

$p = 0.28$); over the entire study period, patients with u5-HIAA levels of 7–100, 101–200, 201–300, and >300 mg/24 h had mortality rates of 7.4% ($n = 2/27$), 12.0% ($n = 3/25$), 26.1% ($n = 6/23$), and 16.7% ($n = 2/12$), respectively.

Three studies only included patients who underwent valve replacement surgery [46–48] and 9 studies reported the number of patients with CS or CHD who received valve replacements [15, 16, 18, 20, 22, 40, 44, 45, 49]. Of these, 2 studies correlated the association of 5-HIAA levels with valve replacement surgery [20, 45]. Møller et al. [20] reported 32 patients referred for valve replacement, noting that these patients had significantly higher u5-HIAA levels at baseline ($p = 0.01$) and at their highest recorded value ($p = 0.03$) versus patients with ≤25% change in their echocardiogram ($n = 46$). In contrast, Møller et al. [45] reported that in patients undergoing cardiac surgery for dysfunctional valves ($n = 87$), u5-HIAA levels were not significantly different versus medically treated patients ($n = 113$; $p = 0.83$).

Quality of Reporting

The 31 studies identified by this review were generally well reported, as assessed by the STROBE checklist (online suppl. data; Table S5) [13]. However, most studies published in congress proceedings did not provide sufficient information to judge their quality [24–27, 38, 41–43]. Additionally, fewer than half of the captured studies described any efforts to reduce bias in their analyses [17, 20–23, 34, 36, 37, 39, 45, 48], only 4 studies explained how missing data were addressed [34, 36, 37, 39, 49], only 1 study addressed patients lost to follow-up [23], and only 4 studies indicated the number of participants with missing data for variables of interest [30, 34, 36, 37, 39].

Discussion

We identified over 30 studies on CHD and 5-HIAA levels in this comprehensive and systematic search of medical literature databases, article reference lists, and abstracts from relevant congresses, allowing us to conduct an up-to-date review of the evidence regarding the relationship between 5-HIAA and CHD. CHD incidence and prevalence varied widely between the included studies, with older studies tending to report higher estimates of prevalence and incidence. This could be a result of the less effective management of CS among patients in older studies, as somatostatin analogues may have helped prevent CHD in more recent years [50].

The large range of CHD incidence estimates could also be a result of variation across the study populations. Three studies investigated patients who were referred for echocardiographic evaluation due to suspicion of CHD [16, 20, 25, 27], and reported incidence estimates of 56% [16], 49% [20], and 40% [25, 27], respectively. This is higher than the median CHD incidence of 24% taken across all the identified studies and is likely to be due to selection bias. A number of other studies, including those reported by Himelman et al. [15], Hoffmann et al. [18], and Ardill et al. [38], gave high incidence estimates but had small sample sizes.

A small number of studies conducted multivariate analyses to compare the risk of death in patients with and without CHD. Westberg et al. [40] found the risk of death to be higher in patients with TR relative to those without (determined by echocardiography). Norlén et al. [36, 37] and Toumpanakis et al. [41–43] reported the risk of death to be significantly higher in patients with CHD, but

Bergestuen et al. [35] did not. Both Bergestuen et al. [35] and Toumpanakis et al. [41–43] examined larger study populations and patients with NETs rather than CS specifically, which could have affected the reported results. For example, Bergestuen et al. [35] investigated the influence of CHD on survival in a relatively large number of patients with NETs who did not have liver metastases or CS. Contrary to the results obtained, the absence of liver metastases and CS would be expected to lead to a longer survival time and potentially a bigger difference in mortality between patients with and without CHD [35]. However, the analysis did not take into account factors other than CHD that could influence patient survival. Contrastingly, Toumpanakis et al. [41–43] adjusted for tumour grade, metastases, and age in their analysis; however, there was a discrepancy between the reported SE and the 95% CI estimated in our analysis, meaning that the results of this study should be interpreted with caution.

In this SLR, u5-HIAA was found to be consistently higher in patients with CHD compared with those without, and all but 1 of the 6 studies investigating the association between 5-HIAA levels and CHD found that higher levels were significantly associated with disease progression [17, 20, 22, 23, 39]. Increased u5-HIAA levels were also associated with increased mortality in the study by Weingarten et al. [48], although the sample size was small, and no statistically significant trend was observed. Overall, these data suggest that 5-HIAA may be a useful prognostic marker for CHD and disease progression in patients with CS. A recently conducted narrative review identified a similar body of evidence to this systematic review, corroborating these findings [6].

Taken together, the results of this review indicate that elevated levels of u5-HIAA are associated with increased probability of CHD diagnosis, disease progression, and mortality. This conclusion is supported by a recent systematic review and meta-analysis that reported a quantifiable relationship between increasing u5-HIAA levels in patients with NETs and higher risk of 1-year mortality [51]. There is a need for consistent and practical guidelines for the screening, diagnosis, and management of CHD in clinical practice. However, a consensus on how to avoid the development of CHD among patients with NETs is lacking, in particular for those who also have CS. The reliance on standard echocardiography to diagnose CHD, particularly in older studies, should be considered when comparing with studies that have employed additional criteria to diagnose and identify patients. Alongside 5-HIAA, N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been demonstrated as a useful diagnostic and prognostic biomarker for CHD and may be considered in future investigations [6]. The surveillance and management of CHD will become increasingly important as patients with NETs live longer as more effective treatments are developed.

A limitation of the current review was the heterogeneity of the included studies, particularly in terms of study design, population sample size and study duration. This may have been further exacerbated by the high level of heterogeneity in the clinical manifestation of NETs between patients [52]. In addition, only some of the studies reported exclusively on patients with CS and CHD. This is an important consideration, as patients with non-secreting NETs or without liver metastases are at significantly reduced risk of developing CHD [1, 6]. Ultimately, this heterogeneity prevented any meta-analysis from being conducted. Nevertheless, several studies consistently reported a link between 5-HIAA levels, CHD diagnosis, and their negative impact on patient prognosis, supporting the conclusion that 5-HIAA is a predictive factor for CHD.

All except one of the included studies relied on urine samples to ascertain 5-HIAA levels [23]. Urinary sampling generally requires collection over a 24-hour period, and factors such as patient diet and incomplete urine collection may impact measurements, introducing variability. Furthermore, it is likely that older studies relied on methods with decreased specificity versus contemporary literature. Harmonisation of methods between studies, and the employment of more sophisticated methods such as plasma or serum 5-HIAA sampling would be beneficial for future research; these methods are generally preferred by patients versus 24-hour collections and have been shown to be consistent with u5-HIAA measurements provided that renal function has been considered [53].

Non-English language publications were excluded unless they had sufficient information in their English abstracts. However, of the small number of non-English language articles that were identified in the database searches, most were of an irrelevant publication type or study design (e.g., case study or narrative review); hence, only a limited proportion of these non-English articles may have had outcomes that would have been of interest to this review.

Conclusions

Although the heterogeneity and individual limitations of the included studies should be taken into consideration when interpreting the results of this review, the identified evidence indicates that elevated 5-HIAA levels are linked to an increased likelihood of CHD development and disease progression, and an increased risk of mortality. CHD was also found to be a significant predictor of death in a number of studies. The development of standardised screening tools for CHD and careful management of 5-HIAA levels could be important considerations for future clinical practice, and beneficial for this patient population.

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Data Sharing Statement

This study is an SLR and no novel data were generated. All data relevant to the study are either included in the article or uploaded as supplementary information.

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