JACC: CARDIOVASCULAR IMAGING VOL. 6, NO. 1, 2013

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2012.08.012

CME

IVC Diameter in Patients With Chronic Heart Failure

Relationships and Prognostic Significance

Pierpaolo Pellicori, MD, Valentina Carubelli, MD, Jufen Zhang, PhD, Teresa Castiello, MD, Nasser Sherwi, MSc, MD, Andrew L. Clark, MA, MD, John G. F. Cleland, MD

Cottingham, Kingston upon Hull, United Kingdom

JACC: CARDIOVASCULAR IMAGING CME

CME Editor: Ragavendra R. Baliga, MD

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CME Objective for This Article: At the end of this activity the reader should be able to: 1) understand relations between inferior vena cava (IVC) diameter and other markers of prognosis in patients with chronic heart failure; 2) understand that measurements of right heart function and upstream consequences of right ventricular dysfunction might be an important determinant of prognosis, even when patients have preserved left ventricular systolic function; and 3) understand the role of measuring IVC diameter in out-patients with chronic heart failure, particularly when measurements of plasma natriuretic peptides are not available.

CME Editor Disclosure: *JACC: Cardiovascular Imaging* CME Editor Ragavendra R. Baliga, MD, has reported that he has no relationships to disclose.

Author Disclosure: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz)

CME Term of Approval:
Issue Date: January 2013
Expiration Date: December 31, 2014

From the Department of Academic Cardiology, Hull and East Yorkshire Medical Research and Teaching Centre, Castle Hill Hospital, Cottingham, Kingston upon Hull, United Kingdom. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 12, 2012; revised manuscript received August 1, 2012, accepted August 2, 2012.

IVC Diameter in Patients With Chronic Heart Failure

Relationships and Prognostic Significance

OBJECTIVES The aim of this study was to assess the relation between inferior vena cava (IVC) diameter, clinical variables, and outcome in patients with chronic heart failure (HF).

BACKGROUND The IVC distends as right atrial pressure rises. Therefore it might represent an index of HF severity independent of left ventricular ejection fraction (LVEF). The relation between IVC diameter and other clinical variables and its prognostic significance in patients with HF has not been explored.

METHODS Outpatients attending a community HF service between 2008 and 2010 were enrolled. Heart failure was defined as the presence of relevant symptoms and signs and objective evidence of cardiac dysfunction: either LVEF <45% or the combination of both left atrial dilation (≥4 cm) and raised amino-terminal pro-brain natriuretic peptide (NT-proBNP) ≥400 pg/ml. Patients were followed for a median of 567 (interquartile range: 413 to 736) days. The primary composite endpoint was cardiovascular death and HF hospitalization.

RESULTS Among the 693 patients enrolled, median age was 73 years, 33% were women, and 568 had HF. Patients with HF in the highest tertile of IVC diameter were older; had lower body mass index; were more likely to have atrial fibrillation and to be treated with diuretics; and had larger left atrial volumes, higher pulmonary pressures, and less negative values for global longitudinal strain. The LVEF and systolic blood pressure were similar across tertiles of IVC diameter. The IVC diameter and log [NT-proBNP] were correlated ($r = 0.55$, $p < 0.001$). During follow-up, 158 patients reached a primary endpoint. In a multivariable Cox regression model, including NT-proBNP, only increasing IVC diameter, urea, and the trans-tricuspid systolic gradient independently predicted a poor outcome. Neither global longitudinal strain nor LVEF were adverse predictors.

CONCLUSIONS In patients with chronic HF with or without a reduced LVEF, increasing IVC diameter identifies patients with an adverse outcome. (J Am Coll Cardiol Img 2013;6:16–28) © 2013 by the American College of Cardiology Foundation

Heart failure (HF) is a common and growing problem. The prognosis remains poor despite the identification of effective treatments, at least for patients with left ventricular systolic dysfunction (LVSD) (1). Considerable efforts have been made to stratify patient risk either to identify patients with a poor prognosis in whom closer surveillance or more intense treatment might improve outcome or to identify potential mechanisms driving outcome that might be targets for therapy. Indeed, the use of LVSD—usually defined as a reduced left ventricular ejection fraction (LVEF)—as an inclusion criterion in clinical trials arose from such concepts: patients with low LVEF clearly had cardiac dysfunction as a cause of symptoms, were at high risk of future events, and had a target for interventions.

The lack of widely accepted objective measures of cardiac dysfunction other than LVEF has hampered and continues to hamper clinical research in patients with HF who do not have LVSD (2). However, data now suggest that patients who have a clinical diagnosis of HF and other objective evidence of cardiac dysfunction (such as left atrial [LA] dilation or raised plasma concentrations of natriuretic peptides [3]) have a poor prognosis whether or not LVEF is low. In turn, this suggests that it might be raised cardiac filling pressures rather than reduced LV contractility that is the major determinant of prognosis.

Right ventricular (RV) function might be a determinant of outcome in HF (4,5). Just as previous work on the left heart has focused on systolic function, so work on the right heart has focused on RV systolic function rather than on the upstream consequences of ventricular dysfunction and tricuspid regurgitation. The jugular venous pressure

(JVP) is a measure of right atrial pressure, but its evaluation by physical examination is unreliable (6). Echocardiographic assessment of inferior vena cava (IVC) diameter is simple and might be an objective, quantifiable measure of right atrial pressure (7). However, its relationship with other clinical variables and its potential prognostic role have received little attention.

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METHODS

Study population. Consecutive outpatients with chronic HF attending a specialist community clinic between November 2008 and March 2010 were enrolled. Heart failure was defined as symptoms with or without signs of HF, supported by objective evidence of cardiac dysfunction: either a LVEF ≤45% or the combination of both LA dilation (≥4 cm diameter in the parasternal long axis) and a plasma concentration of amino-terminal pro-brain natriuretic peptide (NT-proBNP) ≥400 pg/ml.

Patients provided a detailed clinical history, and blood tests (including hematology, biochemistry profile, and NT-proBNP), electrocardiograms, and echocardiograms were obtained on the same day. Ischemic heart disease was defined as a previous history of myocardial infarction or angiographic evidence of significant coronary artery disease. Hypertension was based on prior medical history or systolic blood pressure >140 mm Hg. Patients in atrial fibrillation or atrial flutter were grouped as "AF."

A novel congestion score was constructed, on the basis of lung auscultation (normal, presence of basal, mid-zone or diffuse crepitation), JVP (not visible, raised 1 to 4 cm, raised to earlobe), peripheral edema (none, ankles, below or above knees), and liver examination (not palpable, palpable), with 1 point attributed for each degree of severity. Patients with a score of 3 or more of a possible score of 9 were defined as congested.

Patients were managed according to the National Institute for Health and Clinical Excellence Guidelines (8).

Data regarding hospital stays and death were collected from the electronic systems of the hospital, supplemented by information from patients and their family doctors. The primary outcome was a composite of admission for worsening HF or cardiovascular (CV) death. Admission for HF was defined as an admission for worsening of relevant symptoms resulting in substantial intensification of treatment for HF. If there was an in-hospital CV death, the outcome was reported as CV death rather than HF admission and date of death used for analysis. To avoid errors due to the attribution of cause of death, we also considered the secondary endpoint of all-cause mortality (98 deaths in total).

Echocardiographic measurements. Echocardiography was performed by an experienced operator in accordance with the recommendations of the British Society of Echocardiography (9) with a Vivid Five or Seven (GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom) system. Echocardiograms were retrospectively reviewed by a single operator (P.P.) blinded to other patient details. The LVEF was measured with Simpson's biplane method. The left atrial volume was indexed to body surface area (LAVI). Tricuspid annular plane systolic excursion was used to assess RV systolic function. The trans-tricuspid systolic gradient was also measured.

A digital loop was acquired from apical 2-, 3-, and 4-chamber views at frame rates of 40 to 80 frames/s to assess LV longitudinal strain. Peak systolic strain was defined as the peak negative value on the strain curve during the entire cardiac cycle. An 18-segment model of the LV was used, and values from basal, medium, and apical segment of each wall were then averaged. Global longitudinal strain (GLS) values were reported if 12 or more LV segments in a given patient could be analyzed: analysis was not possible for 13 patients (2%).

With the patient supine, the maximum IVC diameter during the respiratory cycle was measured approximately 3 cm before merger with the right atrium. It is common to index echocardiographic variables to body size. We tested the association between IVC diameter and age, height, weight, body mass index, and body surface area in the 125 subjects with no evidence of HF. None of the variables correlated with IVC diameter, and so we report the un-indexed IVC diameter only.

Statistical methods. Fifty IVC measurements were randomly selected and measured separately by 2 experienced operators blind to each other's results (P.P. and V.C.). The reproducibility and internal consistency of the IVC measurements were tested

ABBREVIATIONS AND ACRONYMS

CV = cardiovascular
GLS = global longitudinal strain
IVC = inferior vena cava
IQR = interquartile range
JVP = jugular venous pressure
LAVI = left atrial volume indexed to body surface area
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
LVSD = left ventricular systolic dysfunction
NT-proBNP = N-terminal B-type natriuretic peptide
ROC = receiver-operating characteristic
RV = right ventricle/ventricular
SHF = systolic heart failure

with Bland-Altman plots and Cronbach's alpha method, respectively.

Categorical data are presented as percentages; normally distributed continuous data are presented as mean ± SD; non-normally distributed variables are presented as median and interquartile range (IQR). The relations between IVC diameter and other variables were assessed by Pearson, Spearman and Point-biserial correlation coefficients. Patients were grouped as: those without evidence of cardiac dysfunction; and, for patients with HF, by IVC diameter tertile. One-way analysis of variance and Kruskal-Wallis tests were used to compare continuous variables between groups, and chi-squared tests were used for categorical variables. Simple and multiple linear regression models were used to identify variables associated with IVC diameter. Only variables significantly associated with IVC diameter in univariable analysis ($p < 0.05$) were entered into the multivariable analysis. Log transformation of NT-proBNP, urea, and high-sensitivity C-reactive protein were used to satisfy the model assumptions.

Associations between variables and prognosis were assessed with Cox proportional hazards models. Because we had only 158 primary outcome events, we chose 8 candidate variables of interest in addition to IVC diameter and NT-proBNP to avoid over-fitting (10). To investigate the prognostic value of IVC diameter compared with a more extensive list of prognostic variables, we repeated the exercise with a more robust dataset, recognizing the risk of over-fitting. Three different multivariable models were tested. The first included both log [NT-proBNP] and IVC diameter and then each of them separately. Forward and backward procedures were used to determine which independently predicted the primary composite outcome. Treatment variables were not included in the model, because these are confounded by indication (patients who are sicker might be more likely to receive some treatments and less likely to tolerate others) and will vary over time.

Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome. C-statistics (area under receiver-operating characteristic [ROC] curves) were used to compare log [NT-proBNP] and IVC diameter as predictors of prognosis at 1 year for the primary and secondary endpoints. The method also was used to compare IVC diameter and other key echocardiographic measures as predictors of prognosis at 1 year for the primary outcome. For comparison of correlated ROC areas the method described by Cleves (11) was used.

Analyses were performed with SPSS and Stata software; a 2-sided p value <0.05 was considered statistically significant.

The study conforms to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All subjects gave their written informed consent.

RESULTS

Patient characteristics. Of patients enrolled (721), 4 were excluded because NT-proBNP results were not available and 24 (3%) were excluded because of poor IVC visualization. Data for the remaining patients (n = 693) are shown in Table 1. Three hundred seventy-two patients (53%) had systolic heart failure (SHF) (LVEF ≤45%), 196 (29%) had HF with preserved LVEF (LVEF >45%, with both a dilated LA and raised NT-proBNP), and 125 (18%) did not fulfill the criteria defining cardiac dysfunction and were considered not to have HF.

IVC measurements. Internal consistency (Cronbach's alpha = 0.993 with 95% confidence interval [CI]: 0.989 to 0.996) and reproducibility (Bland Altman plot: mean difference = −0.040, 95% limits of agreement: −2.480 to 2.400 mm) of measurements of IVC diameter were good. The distribution of IVC diameter for patients with and without HF is shown in Figure 1.

Patients in the highest tertile of IVC diameter were older, had lower body mass index, and were more likely to have atrial fibrillation and to be treated with diuretics. They were more symptomatic, presented more signs of congestion, and had higher NT-proBNP plasma levels. They also had larger LA diameters and volumes, more mitral and tricuspid regurgitation, more severe RV dysfunction, higher pulmonary pressures, and less negative values for GLS. The LVEF and systolic blood pressure were similar across tertiles.

Internal correlates of IVC diameter. In patients with HF (Table 2), there was a correlation between IVC diameter and log[NT-proBNP] overall ($r = 0.55$; $p < 0.001$), in the subgroups with SHF ($r = 0.60$; $p < 0.001$) and HF with preserved ejection fraction ($r = 0.46$; $p < 0.001$), with atrial fibrillation or in sinus rhythm ($r = 0.44$; $p < 0.001$ and $r = 0.55$; $p < 0.001$, respectively), and with estimated glomerular filtration rate above ($r = 0.57$; $p < 0.001$) or below ($r = 0.63$; $p < 0.001$) the median. There

Table 1. Characteristics of Patients by Diagnosis and by Tertiles of IVC Diameter

Variable	Total (n = 693)	No HF (n = 125)	HF (n = 568)	p Value	HF IVC Lowest Tertile (n = 190)	HF IVC Mid-Tertile (n = 189)	HF IVC Highest Tertile (n = 189)	p Value
IVC, mm	18 (16–22)	15 (14–16)	19 (16–23)	<0.01	16 (15–16)	19 (18–20)	24 (23–27)	NA
Clinical data								
Age, yrs	73 (12)	68 (15)	73 (11)	0.01	71 (12)	74 (10)	76 (11)	<0.01
Men	468 (67)	66 (53)	402 (71)	<0.01	133 (70)	132 (70)	137 (72)	0.82
NYHA functional class								
I	125 (18)	34 (27)	91 (16)		41 (22)	31 (16)	19 (10)	<0.01
II	328 (47)	55 (44)	273 (48)	0.01	104 (55)	93 (49)	76 (40)	
III	240 (35)	36 (29)	204 (36)		45 (24)	65 (34)	94 (50)	
IHD	407 (59)	51 (41)	356 (63)	<0.01	123 (65)	129 (68)	104 (55)	0.02
DM	198 (29)	30 (24)	168 (30)	0.12	61 (32)	57 (30)	50 (27)	0.47
Hypertension	409 (59)	85 (68)	324 (57)	0.02	112 (59)	110 (58)	102 (54)	0.57
Smoker	113 (16)	18 (14)	95 (17)	0.31	38 (20)	34 (18)	23 (12)	0.11
Atrial fibrillation	233 (34)	5 (4)	228 (40)	<0.01	34 (18)	71 (38)	123 (65)	<0.01
COPD	94 (14)	27 (21)	67 (12)	<0.01	17 (9)	29 (15)	21 (11)	0.15
SBP, mm Hg	130 (24)	135 (21)	128 (24)	<0.01	131 (24)	128 (23)	127 (26)	0.29
Heart rate, beats/min	72 (15)	72 (13)	72 (15)	0.94	71 (12)	73 (14)	73 (18)	0.26
BMI, kg/m^2	29 (6)	31 (7)	29 (6)	<0.01	30 (6)	29 (6)	28 (5)	<0.01
Congestion ≥3	95 (14)	13 (10)	82 (14)	0.15	9 (5)	21 (11)	52 (28)	<0.01
Blood results								
Creatinine, umol/l	100 (82–131)	86 (73–108)	104 (84–136)	<0.01	99 (82–120)	105 (84–141)	113 (86–146)	<0.01
Urea, mmol/l	7.0 (5.2–9.8)	5.3 (4.1–7.7)	7.2 (5.5–10.0)	<0.01	6.6 (5.2–9.3)	7.1 (5.5–10.0)	8.1 (6.1–11.9)	<0.01
eGFR, ml/min/1.73 m^2	65 (27)	78 (29)	62 (26)	<0.01	66 (22)	63 (28)	58 (26)	0.01
Haemoglobin, g/dl	13.2 (1.8)	13.4 (1.6)	13.1 (1.8)	0.09	13.5 (1.7)	13.2 (1.7)	12.7 (1.9)	<0.01
Albumin, g/l	38 (3)	39 (4)	38 (3)	0.03	38 (3)	38 (3)	37 (4)	<0.01
Bilirubin, μmol/l	14 (11–18)	13 (10–15)	14 (12–19)	<0.01	13 (11–16)	14 (11–18)	17 (13–22)	<0.01
Cholesterol, mmol/l	4.3 (1.1)	4.6 (1.1)	4.2 (1.1)	<0.01	4.4 (1.2)	4.2 (1.1)	4.0 (1.1)	<0.01
NT-proBNP, ng/l	997 (329–2,291)	160 (59–274)	1,331 (602–2,883)	<0.01	537 (294–1,101)	1,437 (854–2,414)	3,095 (1,627–5,547)	<0.01
hsCRP, mg/l	3.6 (1.5–7.3)	3.6 (1.6–6.8)	3.4 (1.5–7.6)	0.58	2.8 (1.2–5.8)	3.3 (1.4–8.0)	4.8 (2.1–9.1)	0.15
Medications								
Beta-blocker	499 (72)	61 (49)	438 (77)	<0.01	159 (84)	146 (77)	133 (70)	<0.01
ACE inhibitor or ARB	572 (83)	90 (72)	482 (85)	<0.01	162 (85)	169 (89)	151 (80)	0.03
Aldosterone antagonist	227 (33)	21 (17)	206 (36)	<0.01	68 (36)	69 (37)	69 (37)	0.99
Loop diuretic	526 (76)	80 (64)	446 (79)	<0.01	133 (70)	155 (82)	158 (84)	<0.01
Statin	441 (64)	74 (59)	367 (65)	0.15	132 (70)	129 (68)	106 (56)	0.01
Antiplatelets	361 (52)	66 (53)	295 (52)	0.47	117 (62)	96 (51)	82 (43)	<0.01
Digoxin	148 (21)	3 (2)	145 (26)	<0.01	27 (14)	51 (27)	67 (35)	<0.01
Warfarin	194 (28)	7 (6)	187 (33)	<0.01	38 (20)	64 (34)	85 (45)	<0.01
CRT	34 (5)	0	34 (6)	0.04	8 (4)	11 (6)	15 (8)	0.31
ICD	52 (7)	3 (2)	49 (9)	0.02	17 (9)	14 (7)	18 (9)	0.75

Continued on next page

Table 1. Continued

Variable	Total (n = 693)	No HF (n = 125)	HF (n = 568)	p Value	HF IVC Lowest Tertile (n = 190)	HF IVC Mid-Tertile (n = 189)	HF IVC Highest Tertile (n = 189)	p Value
Echocardiographic data								
LVEDD, mm	56 (10)	47 (7)	58 (9)	<0.01	57 (9)	59 (10)	59 (10)	0.12
LVEDV, ml	155 (73)	97 (33)	167 (73)	<0.01	156 (67)	170 (76)	176 (74)	0.03
LVEF	45 (14)	59 (6)	42 (13)	<0.01	44 (11)	40 (13)	42 (15)	0.09
GLS	−10.8 (4.6)	−15.9 (2.6)	−9.6 (4.1)	<0.01	−10.5 (3.7)	−9.2 (4.1)	−9.0 (4.5)	<0.01
LA diameter, mm	43 (8)	37 (6)	45 (7)	<0.01	42 (6)	45 (8)	48 (7)	<0.01
LA area, mm^2	24 (8)	18 (5)	26 (8)	<0.01	22 (5)	25 (8)	30 (7)	<0.01
LAVI, ml/m^2	43 (22)	27 (12)	47 (23)	<0.01	35 (13)	46 (23)	60 (24)	<0.01
TAPSE, mm	18.5 (4.6)	21.5 (4.1)	17.9 (4.5)	<0.01	19.5 (4.1)	18.0 (4.0)	16.2 (4.4)	<0.01
TR gradient, mm Hg	27 (11)	21 (9)	28 (11)	<0.01	22 (6)	27 (9)	36 (12)	<0.01
Mitral regurgitation								
Mild	189 (27)	12 (10)	177 (31)	<0.01	45 (24)	67 (35)	65 (34)	<0.01
Moderate/severe	104 (15)	5 (4)	99 (17)		9 (5)	33 (17)	57 (30)	
Tricuspid regurgitation								
Mild	141 (20)	6 (5)	135 (24)	<0.01	15 (8)	50 (26)	70 (37)	<0.01
Moderate/severe	52 (7)	2 (1)	50 (9)		2 (1)	6 (3)	42 (22)	

Values are mean ± SD if the variable is normally distributed and median and interquartile range if not. The statistical difference between variables is given for the comparison between patients with and without heart failure, and between tertiles of inferior vena cava (IVC) diameter in the heart failure (HF) population only. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; GLS = global longitudinal strain; hsCRP = high sensitivity C-reactive protein; ICD = implantable cardioverter defibrillator; IHD = ischemic heart disease; LA = left atrium; LAVI = left atrial volume index; LVEDD = left ventricle end-diastolic diameter; LVEDV = left ventricle end diastolic volume; LVEF = left ventricular ejection fraction; NTproBNP = N-terminal B-type natriuretic peptide; NYHA = New York Heart association; SBP = systolic blood pressure; TAPSE = tricuspid annular plane systolic excursion; TR gradient = trans-tricuspid systolic gradient.

was a relation between IVC diameter and bilirubin ($r = 0.32$; $p < 0.001$) and, inversely, with albumin ($r = -0.20$; $p < 0.001$). The IVC diameter correlated with congestion index ($r = 0.34$, $p < 0.001$) and with the individual signs used to derive that score (peripheral edema: $r = 0.30$; $p < 0.001$; lung crepitation: $r = 0.17$; $p < 0.001$; JVP: $r = 0.31$; $p < 0.001$; hepatomegaly: $r = 0.22$; $p < 0.001$). There was no relation between IVC diameter and measures of LV volumes or systolic function. There was a weak correlation between IVC diameter and GLS ($r = 0.10$; $p = 0.03$).

In patients with HF, age, increasing log [NT-proBNP], LAVI and pulmonary artery pressures, atrial fibrillation, and tricuspid regurgitation were independently associated with increasing IVC diameter (Table 2) (overall $R^2 = 0.53$).

Admission for worsening HF or CV death. Patients with HF (n = 568) were followed-up for a median of 567 (IQR: 413 to 736) days. The minimum follow-up in survivors was 365 days. There were 158 events (78 patients were admitted to hospital with HF, and 80 died due to CV causes, of which 48 were attributed to HF, 26 to out of hospital sudden death, 5 to myocardial infarction, and 1 to stroke). Neither LVEF nor GLS predicted events (Table 3).

The IVC diameter was the strongest predictor of adverse prognosis in the univariable analysis for both groups of patients with HF (SHF: hazard ratio: 1.17, 95% CI: 1.13 to 1.22, Wald chi-square: 71.20; HFNEF: hazard ratio: 1.17, 95% CI: 1.11 to 1.22, Wald chi-square: 40.12).

In multivariable analysis, the "parsimonious" model (Table 4) identified decreasing systolic blood

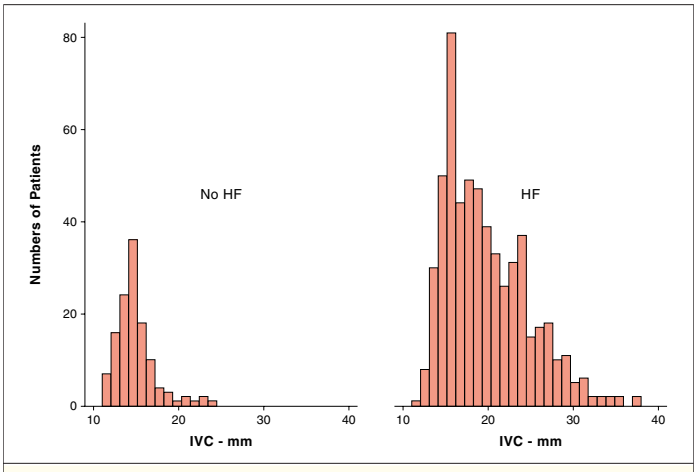

Figure 1. Distribution of IVC Diameter

The distribution of inferior vena cava (IVC) diameter in patients without **(left panel)** or with **(right panel)** heart failure (HF).

Table 2. Variables Associated With IVC Diameter in Patients With Heart Failure (n = 568)

Variables Associated With IVC Diameter	Univariable Analysis		Multivariable Analysis	
	Correlation Coefficient	p Value	Unstandardized Coefficients (95% CI)	t Stat (p Value)
Clinical data				
Age	0.18	<0.01	−0.53 (−0.87 to −0.20)	−3.17 (<0.01)
Men	0.01	0.92		
NYHA functional class	0.25	<0.01		
IHD	−0.07	0.10		
DM	−0.10	0.80		
HTN (or SBP >140 mm Hg)	−0.03	0.55		
Smoker	−0.08	0.05		
Atrial fibrillation	0.42	<0.01	1.52 (0.67 to 2.38)	3.51 (<0.01)
COPD	0.02	0.65		
SBP, mm Hg	−0.06	0.13		
Heart rate, beats/min	0.07	0.12		
BMI, kg/m^2	−0.10	0.02		
Congestion ≥3	0.34	<0.01		
Blood test				
Creatinine, umol/l	0.15	<0.01		
Urea*, mmol/l	0.19	<0.01		
eGFR, ml/min/1.73 m^2	−0.14	<0.01		
Hemoglobin, g/dl	−0.21	<0.01		
Albumin, g/l	−0.20	<0.01		
Bilirubin, μmol/l	0.32	<0.01		
Cholesterol, mmol/l	−0.19	<0.01		
NT-proBNP*, ng/l	0.55	<0.01	2.55 (1.69 to 3.40)	5.87 (<0.01)
hsCRP*, mg/l	0.04	0.36		
Echocardiographic data				
LVEDD, mm	0.05	0.27		
LVEDV, ml	0.06	0.15		
LVEF, %	0.02	0.61		
GLS, %	0.10	0.02		
LA diameter, mm	0.38	<0.01		
LA area, mm^2	0.47	<0.01		
LAVI, ml/m^2	0.44	<0.01	0.02 (0.08 to 0.40)	2.99 (<0.01)
TAPSE, mm	−0.34	<0.01		
TR gradient, mm Hg	0.54	<0.01	0.09 (0.05 to 0.12)	4.95 (<0.01)
Mitral regurgitation	0.33	<0.01		
Tricuspid regurgitation	0.48	<0.01	1.24 (0.63 to 1.86)	3.98 (<0.01)

Results were obtained from univariable and multivariable linear regression models. The first column on the left (univariable analysis) represents the correlation between IVC diameter and the variables studied. A log transformation was also done for variables labelled with *before conducting the analysis to satisfy the model assumptions. The columns for the multivariable analysis (right) show the coefficients for slope of the linear relation between all the variables independently associated with IVC diameter (R^2= 0.53).
CI = confidence interval; HTN = Hypertension; other abbreviations as in Table 1

pressure, increasing New York Heart Association functional class, urea, IVC diameter, and the transtricuspid systolic gradient as independent predictors of poor outcome. When IVC diameter was excluded, log [NT-proBNP] and LAVI entered the model. When a more extensive dataset was used (Table 3) and both log [NT-proBNP] and IVC diameter were included, IVC diameter but not log [NT-proBNP] was independently associated with a poor outcome.

The Kaplan-Meier curves (Fig. 2) show that patients in the highest tertile of IVC diameter had approximately a 40% risk of an adverse event within the first year and that patients with HF in the lowest tertile of IVC diameter had a similar outcome to subjects without HF.

Table 3. Univariable and Multivariable Cox Regression Models for the Composite Endpoint CV Death or HF Hospitalization in Patients With HF (n = 568 Patients With Heart Failure Who had 158 Events)

	Univariable Analysis			Multivariable Analysis			Multivariable Analysis NT-proBNP Excluded IVC Excluded		
Variables	HR (95% CI)	Wald Chi-Square	p Value	HR (95% CI)	Wald Chi-Square	p Value	HR (95% CI)	Wald Chi-Square	p Value
Clinical data									
Age, yrs	1.03 (1.01–1.05)	15.90	<0.01						
Men	1.00 (0.71–1.41)	0.01	0.99						
NYHA functional class III vs. I/II	2.40 (1.75–3.33)	30.08	<0.01	1.65 (1.15–2.37)	7.34	<0.01	1.66 (1.16–2.40)	7.56	<0.01
							1.58 (1.09–2.28)	5.96	0.02
IHD	0.88 (0.63–1.19)	0.77	0.38						
DM	1.01 (0.71–1.41)	0.01	0.97						
Hypertension or SBP >140 mm Hg	0.61 (0.45–0.84)	7.47	<0.01	0.67 (0.45–0.98)	4.12	0.02	0.67 (0.45–0.98)	4.20	0.04
Atrial fibrillation	1.75 (1.28–2.40)	12.44	<0.01						
COPD	1.05 (0.65–1.70)	0.04	0.84						
SBP, mm Hg	0.99 (0.98–1.00)	7.60	<0.01						
Heart rate, beats/min	1.01 (0.99–1.02)	1.29	0.25						
BMI, kg/m^2	0.96 (0.93–0.99)	7.73	<0.01						
Congestion ≥3 signs	2.77 (1.94–3.93)	31.80	<0.01						
JVP	2.29 (1.86–2.81)	62.44	<0.01						
Blood test									
Creatinine, umol/l	1.01 (1.00–1.01)	39.28	<0.01						
Urea, mmol/l	1.10 (1.07–1.12)	50.68	<0.01	1.06 (1.02–1.09)	11.27	<0.01	1.06 (1.03–1.09)	13.14	<0.01
							1.05 (1.02–1.08)	8.21	<0.01
eGFR, ml/min/1.73 m^2	0.98 (0.97–0.99)	21.45	<0.01						
Hemoglobin, g/dl	0.77 (0.71–0.84)	35.47	<0.01						
Albumin, g/l	0.89 (0.86–0.93)	29.98	<0.01						
Bilirubin, μmol/l	1.04 (1.01–1.06)	10.30	<0.01						
Cholesterol, mmol/l	0.72 (0.62–0.85)	15.08	<0.01						
Log (NT-proBNP)	4.36 (3.14–6.06)	77.31	<0.01				1.76 (1.05–2.94)	4.67	0.03
hsCRP, mg/l	1.01 (1.00–1.02)	6.88	<0.01						
Echocardiographic data									
IVC, mm	1.17 (1.13–1.20)	112.14	<0.01	1.12 (1.07–1.17)	21.51	<0.001	1.13 (1.08–1.18)	25.48	<0.01
LVEDV, ml	1.00 (0.99–1.00)	1.58	0.21						
LVEDD, mm	1.01 (0.99–1.03)	0.83	0.36						
LVEF, %	0.99 (0.98–1.01)	0.38	0.54						
GLS, %	1.04 (0.99–1.08)	2.93	0.09						
LA diameter, mm	1.04 (1.02–1.06)	16.36	<0.01						
LA area, mm^2	1.04 (1.03–1.06)	31.22	<0.01						
LAVI, ml/m^2	1.02 (1.01–1.02)	44.98	<0.01						
TAPSE, mm	0.90 (0.87–0.93)	30.26	<0.01						
TR gradient, mm Hg	1.05 (1.04–1.06)	84.92	<0.01				1.02 (1.01–1.04)	7.76	<0.01
Mitral regurgitation	1.82 (1.50–2.21)	36.79	<0.01						
MR: moderate vs. mild	2.79 (2.00–3.89)	36.71	<0.01						
Tricuspid regurgitation	2.29 (1.87–2.82)	62.59	<0.01						
TR: moderate vs. mild	4.89 (2.60–5.81)	43.98	<0.01						

In the first column the univariable analysis is shown, the second column shows a multivariable model based on a more robust dataset, which includes both LogNTproBNP and IVC diameter. In the last column 2 different multivariable models have been tested: one excluding logNTproBNP and one excluding IVC diameter.

CV = cardiovascular; HR = hazard ratio; JVP = jugular venous pressure; other abbreviations as in Table 1 and 2.

Table 4. A "Parsimonious" Multivariable Cox Regression Model for the Composite Endpoint of CV Death or HF Hospitalization in Patients With HF

Variables	Multivariable Analysis			Multivariable Analysis IVC Excluded		
	HR (95% CI)	Wald Chi-Square	p Value	HR (95% CI)	Wald Chi-Square	p Value
Age, yrs	1.01 (0.99–1.03)	1.05	0.31	1.01 (0.99–1.02)	0.31	0.57
NYHA functional class III vs. I/II	1.51 (1.08–2.11)	5.83	0.02	1.49 (1.06–2.09)	5.22	0.02
SBP, mm Hg	0.99 (0.98–1.00)	6.26	0.01	0.99 (0.98–1.00)	7.70	<0.01
Urea, mmol/l	1.05 (1.01–1.08)	9.19	<0.01	1.05 (1.01–1.08)	8.45	<0.01
Hemoglobin, g/dl	0.92 (0.83–1.02)	2.31	0.13	0.93 (0.84–1.03)	1.99	0.16
Log [NT-proBNP], pg/ml	1.36 (0.85–2.11)	1.67	0.20	1.85 (1.18–2.89)	7.13	<0.01
IVC, mm	1.10 (1.06–1.14)	26.28	<0.01	—	—	—
LVEF, %	1.00 (0.99–1.02)	0.05	0.82	1.00 (0.99–1.01)	0.09	0.76
LAVI, ml/m^2	1.00 (0.99–1.01)	1.48	0.22	1.01 (1.00–1.01)	4.64	0.03
TR gradient, mm Hg	1.02 (1.00–1.03)	4.09	0.04	1.03 (1.01–1.04)	13.77	<0.01

To avoid over-fitting, 8 candidate variables of interest in addition to IVC diameter and NT-proBNP were chosen. On the left, the model includes IVC. On the right, IVC was excluded. Abbreviations as in Tables 1, 2, and 3.

The ROC curves for outcome at 1 year (Fig. 3) showed no difference between IVC diameter and log [NT-proBNP] ($p = 0.20$). Among other echocardiographic measures, IVC diameter had the greatest area under the curve in predicting survival to 1 year (Fig. 4).

IVC diameter and total mortality. During a median follow-up of 600 (IQR: 449 to 756) days, 98 patients (17%) with HF died. The "parsimonious" model (Table 5) identified decreasing hemoglobin and systolic blood pressure and increasing age, urea, and IVC diameter as independent predictors of mortality. When IVC diameter was excluded, increasing log [NT-proBNP] entered the model. The relation between both IVC diameter and log [NT-proBNP] and 1 year mortality was similar on ROC curve analysis (Fig. 5).

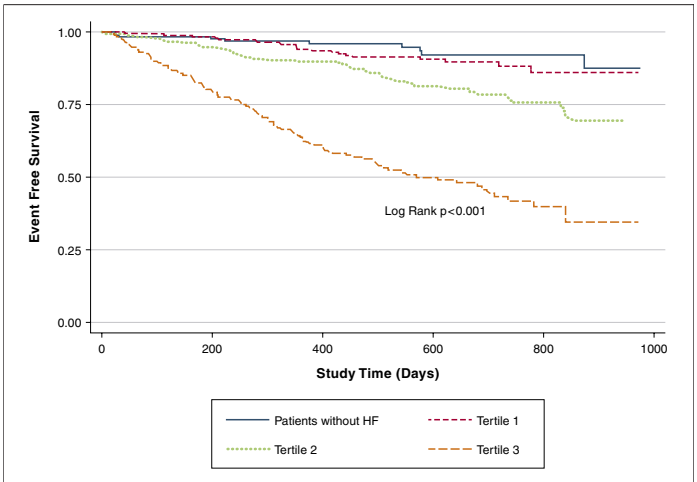

Figure 2. IVC Diameter and Outcome

Kaplan-Meier curves for the primary composite endpoint (heart failure [HF] hospitalization or cardiovascular death) in patients without HF (**solid blue line**) and by tertiles of inferior vena cava (IVC) diameter in patients with HF (**red** is lowest tertile, **green** is mid-tertile, and **orange** is highest tertile). Patients in the lowest tertile of IVC diameter had a rate of events similar to those considered not to have HF. For patients with HF, the hazard ratio for this outcome was 7.02 (95% confidence interval: 4.34 to 11.37; $p < 0.001$) in the highest versus lowest tertile with an approximate 50% probability of hospitalization for worsening HF or cardiovascular death within 18 months estimated from the Kaplan-Meier curve.

DISCUSSION

The clinical diagnosis of HF is fundamentally based on demonstrating objective evidence of cardiac dysfunction in the presence of symptoms, such as breathlessness, and signs, such as peripheral edema. Echocardiographic assessment focusing solely on LV function might be misleading. Many patients with symptoms and signs of HF and with a raised NT-proBNP have no gross abnormality of LV systolic function and yet these patients often respond symptomatically to diuretics, have recurrent admissions for HF, and have a poor prognosis. A broader view of what constitutes cardiac dysfunction leading to HF is required.

If congestion is the hallmark of HF, then distension of the great veins might be the best marker on imaging. The IVC diameter is usually easy to measure in patients with HF and has low inter-observer variation. We have shown that increasing IVC diameter is associated with a worse prognosis.

The IVC diameter is a summary measure of cardiac function as well as a marker of venous congestion. Left ventricular dysfunction, either systolic or diastolic, causes LA hypertension. The pressure is transmitted back through the pulmonary circulation to cause pulmonary arterial hypertension (12) that, in turn, compounds any pre-existing RV dysfunction and exacerbates tricuspid regurgitation.

All of these stresses result in an increase in right atrial pressure and IVC distension. Neuroendocrine activation and a decline in renal perfusion might also cause salt and water retention, leading to congestion even in the absence of gross elevation in atrial pressures.

Our report confirms the findings of Nath et al. (13), who reported IVC diameter in 3,729 patients, almost exclusively men, having echocardiograms at 1 of 3 U.S. Veterans hospitals. Patients with a dilated IVC that did not collapse with inspiration were older, were more likely to have HF (38%), and had a 33% mortality at 1 year, compared with 9% in those with a dilated IVC that collapsed on inspiration and 5% in those who did not have a dilated IVC. However, Nath chose an arbitrary cutoff of 2 cm as a definition of IVC dilation and did not investigate its relation with either body habitus or natriuretic peptides.

Ours is the first study to investigate the relations between IVC diameter and other markers of prognosis in patients with chronic HF. In our study, there was a strong relation between IVC diameter and plasma NT-proBNP levels, perhaps because both reflect a summary measure of cardiac and renal function. Although BNP is secreted predominantly by the LV under normal physiological circumstances (14,15), plasma concentrations increase as pulmonary artery pressure rises and with the development of RV dysfunction (12,16), suggesting that it might be derived from other parts of the heart. The lack of specificity of natriuretic peptides for the diagnosis of HF can be regarded as either a strength or weakness, depending on the circumstances: abnormal results indicate that there is a problem that requires further investigation but not its cause. The IVC diameter might offer diagnostic advantages similar to NT-proBNP as a nonspecific marker of global cardiac dysfunction but might be less influenced by non cardiac factors such as renal dysfunction or AF. Where echocardiography is not available, for instance in primary care, a blood test as the first diagnostic step for suspected HF is convenient and efficient. When echocardiography is available, IVC diameter might provide similar information.

We found that IVC diameter was a strong predictor of prognosis, providing information similar to NT-proBNP (widely considered to be 1 of the most robust prognostic markers in patients with HF). By contrast, no direct measure of LV function contributed prognostic information. The IVC diameter was related to many features of congestion, including clinical signs,

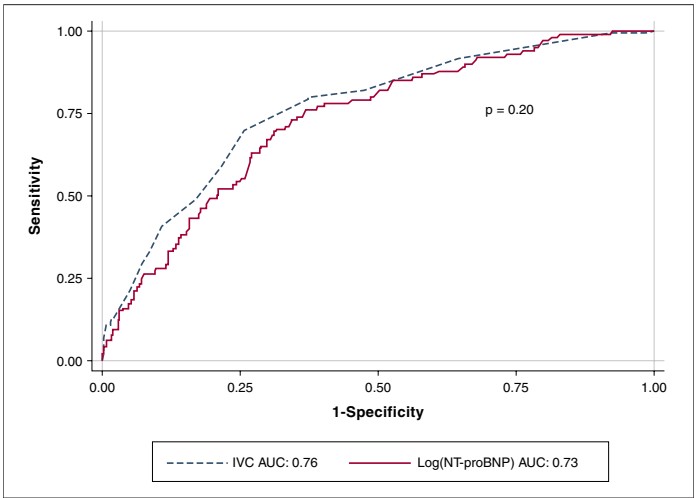

Figure 3. IVC Diameter and Log [NT-proBNP] as Predictors of Outcome

Receiver-operating characteristic curves are used to compare log N-terminal B-type natriuretic peptide (NT-proBNP) and inferior vena cava (IVC) diameter as predictors of prognosis at 1 year for the combined endpoint of heart failure hospitalization and cardiovascular death. The IVC diameter **(blue line)** had a slightly greater area under the curve (AUC) (0.76 with a 95% confidence interval: 0.71 to 0.81) than log [NT-proBNP] (AUC: 0.73, 95% confidence interval: 0.68 to 0.78), but the difference was not statistically significant (p = 0.20).

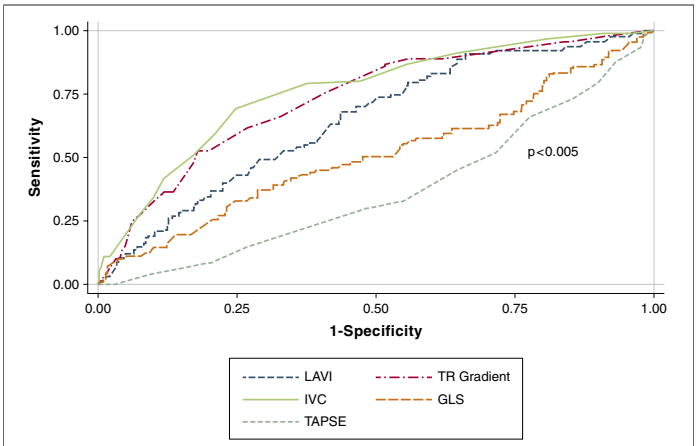

Figure 4. Echocardiographic Measures as Predictors of Outcome

Receiver-operating characteristic curves are used to compare inferior vena cava (IVC) diameter and echocardiographic measures (left atrial volume indexed to body surface area [LAVI], tricuspid annular plane systolic excursion [TAPSE], transtricuspid systolic (TR) gradient, and global longitudinal strain [GLS]) as predictors of prognosis at 1 year for the combined endpoint of heart failure hospitalization and cardiovascular death. The IVC diameter had a greater AUC (0.76 with a 95% confidence interval [CI]: 0.71 to 0.81) than TR gradient (AUC: 0.73, 95% CI: 0.67 to 0.78), LAVI (AUC: 0.64, 95% CI: 0.59 to 0.71), GLS (AUC: 0.51, 95% CI: 0.44 to 0.58), or TAPSE (AUC: 0.37, 95% CI: 0.31 to 0.43). The difference was statistically significant (chi-square = 78.44; $p < 0.001$).

Table 5. A "Parsimonious" Multivariable Cox Regression Model for the Secondary Endpoint of Death for all Causes in Patients With HF

	Multivariable Analysis			Multivariable Analysis IVC Excluded		
Variables	**HR (95% CI)**	**Wald Chi-Square**	**p Value**	**HR (95% CI)**	**Wald Chi-Square**	**p Value**
Age, yrs	1.03 (1.01–1.06)	6.25	0.01	1.03 (1.00–1.06)	4.75	0.03
NYHA functional class I/II vs. III	1.21 (0.80–1.84)	0.81	0.37	1.21 (0.79–1.85)	0.78	0.38
SBP, mm Hg	0.98 (0.97–0.99)	11.10	<0.01	0.98 (0.97–0.99)	10.66	<0.01
Urea, mmol/l	1.04 (1.01–1.08)	5.33	0.02	1.05 (1.01–1.09)	6.89	<0.01
Hemoglobin, g/dl	0.82 (0.72–0.93)	9.13	<0.01	0.83 (0.74–0.94)	8.46	<0.01
Log [NT-proBNP)], pg/ml	1.48 (0.82–2.65)	1.69	0.19	1.92 (1.10–3.36)	5.24	0.02
IVC, mm	1.09 (1.04–1.14)	11.76	<0.01	—	—	—
LVEF, %	1.01 (0.99–1.02)	0.40	0.53	1.01 (0.99–1.02)	0.75	0.38
LAVI, ml/m^2	1.00 (0.99–1.01)	0.84	0.36	1.01 (0.99–1.01)	2.06	0.15
TR gradient, mm Hg	1.00 (0.98–1.02)	0.10	0.75	1.01 (0.99–1.03)	1.65	0.20

To avoid over-fitting, 8 candidate variables of interest in addition to IVC diameter and NT-proBNP were chosen. On the left, the model includes IVC. On the right, IVC was excluded. Abbreviations as in Tables 1, 2, and 3.

decreasing albumin, and renal (17) and hepatic (18) dysfunction.

Our findings also confirm and support the notion that right rather than left heart function might be an important determinant of prognosis in patients with HF (19–21). Ambulatory patients with suspected HF have a worse outcome if clinical signs of congestion are present (22) and, in patients with definite HF, high right atrial pressure is associated with an increased risk of progression and mortality for HF (23). Drazner et al. (24) showed that a raised JVP is the only clinical sign associated with raised LV filling pressure. However, the clinical assessment of the JVP varies between doctors (6,25), and the measurement of IVC might be more reliable.

Raised cardiac filling pressure, or "backwards" failure (26), seems at least as important in determining prognosis as a decline in cardiac output, or "forwards" failure.

That an apparently simple measurement is such a strong marker of prognosis raises the possibility that interventions targeting improvement of right rather than left heart function should be explored to find out whether they will improve outcome. However, it is also possible that IVC diameter will improve if any important aspect of cardiac function improves, including LV function or pulmonary vascular resistance.

Study limitations. Our results require independent confirmation by other groups before the prognostic equivalence between NT-proBNP and IVC diameter should be accepted. We did not attempt to explore the diagnostic utility of IVC diameter, because patients were referred from a variety of sources with varying degrees of sophistication in the pre-referral work-up.

We did not measure mitral annulus E/E' ratio, a marker of LA pressure. Although E/E' ratio predicts cardiac events in patients with HF (27), it adds little prognostic information to LA volume (28), which we did measure.

We were surprised not to find any relation between IVC diameter and any measure of body size in normal subjects. We found broadly similar results when testing the relation between IVC

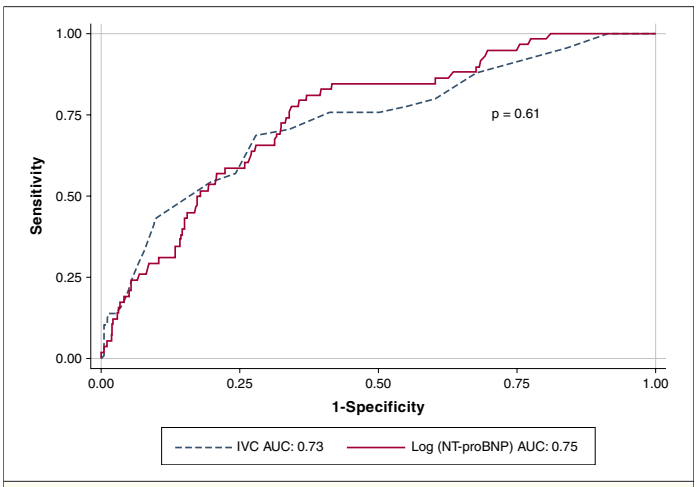

Figure 5. IVC Diameter and Log [NT-proBNP] as Predictors of All-Cause Mortality

Receiver-operating characteristic curves are used to compare log [NT-proBNP] and IVC diameter as predictors of all-cause mortality at 1 year (58 deaths). The AUCs for both variables were similar: IVC diameter **(blue line)** AUC: 0.73 (95% CI: 0.66 to 0.80); log [NT-proBNP] AUC: 0.75 (95% CI: 0.69 to 0.81) (p = 0.61 for the comparison). Abbreviations as in Figures 3 and 4.

diameter corrected for body surface area and outcome as for the un-indexed measurement (data not shown). However, because we have previously shown that body surface area is itself strongly related to outcome, (29) we have chosen to present the raw data for IVC diameter.

The patients without HF who formed our comparator group cannot be considered entirely "normal" as they were referred, because of diagnostic concerns. The use of an NT-proBNP threshold of 400 pg/ml, a value suggested by guidelines that were current at the time (30), might have been too stringent. It is possible that we have excluded some patients with HF on this basis who might have disease that only becomes evident under stress (31,32).

CONCLUSIONS

The IVC diameter is easy to measure and provides similar prognostic information as plasma concentrations of NT-proBNP in outpatients with chronic HF. Its utility as a way of monitoring progression of HF and response to treatment warrants further study.

Reprint requests and correspondence: Dr. Pierpaolo Pellicori, Department of Academic Cardiology, Hull and East Yorkshire Medical Research and Teaching Centre, MRTDS (Daisy) Building, Entrance 2, Castle Hill Hospital, Cottingham, Kingston upon Hull HU16 5JQ, United Kingdom. *E-mail: pierpaolo.pellicori@hey.nhs.uk.*

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Key Words: chronic heart failure ■ inferior vena cava ■ prognosis.

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