Revisiting the obesity paradox in heart failure: Per cent body fat as predictor of biomarkers and outcome

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Abstract

Aims: Obesity defined by body mass index (BMI) is characterized by better prognosis and lower plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) in heart failure. We assessed whether another anthropometric measure, per cent body fat (PBF), reveals different associations with outcome and heart failure biomarkers (NT-proBNP, high-sensitivity troponin T (hs-TnT), soluble suppression of tumorigenesis-2 (sST2)).

Methods: In an individual patient dataset, BMI was calculated as weight (kg)/height (m)2, and PBF through the Jackson–Pollock and Gallagher equations.

Results: Out of 6468 patients (median 68 years, 78% men, 76% ischaemic heart failure, 90% reduced ejection fraction), 24% died over 2.2 years (1.5–2.9), 17% from cardiovascular death. Median PBF was 26.9% (22.4–33.0%) with the Jackson–Pollock equation, and 28.0% (23.8–33.5%) with the Gallagher equation, with an extremely strong correlation (r ¼ 0.996, p < 0.001). Patients in the first PBF tertile had the worst prognosis, while patients in the second and third tertile had similar survival. The risks of all-cause and cardiovascular death decreased by up to 36% and 27%, respectively, per each doubling of PBF. Furthermore, prognosis was better in the second or third PBF tertiles than in the first tertile regardless of model variables. Both BMI and PBF were inverse predictors of NT-proBNP, but not hs-TnT. In obese patients (BMI c 30 kg/m2, third PBF tertile), hs-TnT and sST2, but not NT-proBNP, independently predicted outcome.

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Conclusion: In parallel with increasing BMI or PBF there is an improvement in patient prognosis and a decrease in NT-proBNP, but not hs-TnTor sST2. hs-TnTor sST2 are stronger predictors of outcome than NT-proBNP among obese patients.

Keywords
Obesity, heart failure, natriuretic peptides, troponin, sST2, prognosis

Introduction
Obesity is a growing public health problem and significantly increases the risk of several disorders, including coronary artery disease and heart failure. However, once a patient develops heart failure, overweight and mild-to-moderate obesity are associated with better survival compared with patients with normal weight.

Several explanations have been proposed for this ‘obesity paradox’, which has also been described in other chronic disorders. For example, obese patients tend to be younger, and have greater energy reserves and less muscle depletion. They also display an attenuated response to sympathetic and renin-angiotensin-system activation, and tolerate better drugs for neuroendocrine antagonism because they are often hypertensive at treatment initiation. Higher insulin concentrations may also exert positive effects on the autonomic nervous system and the pituitary-adrenal axis, manifesting as reduced peripheral vascular resistances.

Despite these facts, existence of an obesity paradox has been questioned by considering that all evidence derives from studies using body mass index (BMI), a simple measure that is not informative on the amount and distribution of body fat. Most notably, a recent study on 1738 heart failure patients showed that a higher waist-to-hip ratio (WHR), an indicator of abdominal obesity, predicts a higher risk of death among women. The authors thus challenged the obesity paradox, postulating that ‘fat deposition is patho-physiologically harmful and may be a target for therapy in female patients with heart failure’.

In the field of heart failure biomarkers, another paradox described is that of the decrease in circulating natriuretic peptides among overweight and obese patients. Mechanisms underlying this inverse association between BMI and natriuretic peptides have not been clarified so far, although some possible explanations have been proposed, largely focused on reduced production of B-type natriuretic peptide (BNP) or the N-terminal fraction of pro-BNP (NT-proBNP), rather than their clearance. Importantly, the influence of BMI or body composition on high-sensitivity troponin T (hs-TnT) or soluble suppression of tumorigenesis-2 (sST2), two biomarkers useful for risk stratification in heart failure, has not been established so far.

To clarify these points, in a large individual heart failure patient dataset designed to assess the prognostic value of heart failure biomarkers we evaluated: a) the relationship between BMI and per cent body fat (PBF), as a measure of body composition, and patient prognosis; b) the relationship between BMI and PBF with NT-proBNP, hs-TnT and sST2.

Methods
Search strategy, study selection
In April 2017, studies evaluating hs-TnT and prognosis in chronic heart failure were searched in four databases (Medline, EMBASE, Cochrane Library and Scopus) to perform an individual patient data meta-analysis on hs-TnT and prognosis. For the present analysis, patients with BMI data available were considered (6468 out of 9289, 70%). All patients had data on all-cause death, while information on cardiovascular death was available for 6262 (97%).

Anthropometric measures
BMI was calculated as weight (kg)/height² (m²). Patients were stratified into the following categories, according to the World Health Organization: under-weight (BMI < 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), obesity class I (30–34.9 kg/m²), obesity class II (35–39.9 kg/m²), obesity class III (≥40 kg/m²). PBF was estimated from BMI, gender and age through the Jackson–Pollock and Gallagher equations (Supplemental Material Table 1 online).

Biohumoral evaluation
In all studies NT-proBNP was measured through the ECLIA monoclonal method (Roche Diagnostics), sST2 with the Presage assay, and TnT through a hs- assay (Roche Diagnostics). The analytical
characteristics of these assays are presented in dedicated papers. These biomarkers were dosed in a core laboratory for each study; NT-proBNP and hs-TnT were dosed during each of the six original studies or shortly after their completion, while sST2 was measured on the stored samples. The estimated glomerular filtration rate (eGFR) was calculated through the Chronic Kidney Disease Epidemiology Collaboration equation.

Statistical analysis

IBM SPSS Statistics (version 22, 2013) and R statistical software (http://www.r-project.org/, version 3.4.4) were used. Normal distribution was assessed through the Kolmogorov–Smirnov test; variables with normal distribution were presented as mean standard deviation, while those with non-normal distribution as median and interquartile interval. NT-proBNP, hs-TnT and sST2 were log2-transformed. Mean differences among groups were evaluated through the unpaired Student t test. Categorical variables were compared by the Chi-square test with Yates correction. Pearson’s product moment correlation coefficient (r) was calculated as a measure of linear association between variables. The log-rank test (Mantel–Cox) was used to compare survival times on Kaplan–Meier curves. Cubic spline interpolation was carried out to represent the changes in risk according to biomarker values; five knots were considered. The BMI value for which hazard ratio 1 was chosen as the value corresponding to the inflection point of the curve, above which the slope of the curve becomes steeper. Except for NT-proBNP, hs-TnT and sST2, all univariate predictors of all-cause death with a p value < 0.10 were included in the multivariate analysis: age, gender, ischaemic aetiology, estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class I–II vs. III–IV, hypertension, chronic obstructive pulmonary disease (COPD), diabetes, atrial fibrillation, high-sensitivity C-reactive protein (hs-CRP), therapy with angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (ACEi/ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs). Multicollinearity was searched by calculating the Variance Inflation Factor. The Schoenfeld Residuals Test was used to test the proportional hazard assumption in Cox model; time-dependent variables were used when this assumption was not met. The ‘one-in-10’ rule was followed to avoid model overfitting. In Cox regression analysis, the Fine–Gray model was used to account for mutually exclusive endpoints; non-cardiovascular death was considered as competing risk for cardiovascular death. The net reclassification improvement (with risk categories set at <10%, 10–30% and >30%) and the integrated discrimination improvement were calculated to assess reclassification. Two-tailed p values <0.05 were considered significant.

Results

Population characteristics across categories of body mass index

The main characteristics of patients evaluated (N = 6468) are summarized in Table 1. Median age was 68 years (interquartile interval 58–76), and the majority of patients (n = 5071, 78%) were men, and had heart failure with ischaemic aetiology (n = 3650, 76%). The overall median LVEF was 27% (21–34%), and the vast majority of patients (n = 5848, 90%) had heart failure with reduced ejection fraction. Renal function was moderately impaired, with a median eGFR of 57 mL/min per 1.73 m² (44–68). Median circulating NT-proBNP, hs-TnT and sST2 were 1359 ng/L (513–3229), 18 ng/L (9–33) and 27 ng/mL (20–39), respectively.

Patients in the different BMI categories were heterogeneous in many respects. Most notably, age decreased with increasing BMI, the prevalence of hypertension and diabetes became progressively higher, glomerular filtration rate and LVEF increased, and NT-proBNP decreased (Table 1).

BMI and prognosis

Over a median 2.2-year follow-up (1.5–2.9), 1546 patients (24%) died, and cardiovascular death occurred in 1088 patients, out of 6262 with available data (17%). The shortest survival free from these endpoints was recorded for patients with BMI <18.5 kg/m²; survival increased progressively from underweight to normal weight and overweight patients, and was not significantly different from overweight to grade III obesity (Supplemental Figure 1). When stratifying the population according to the 25 and 30 BMI cut-offs, patients with BMI <25 had a worse prognosis than those with BMI 25–30 or ≥30, whose survival was similar (Supplemental Figure 2). The same conclusion was reached for both male (all-cause death: log-rank 53.1, p <0.001; cardiovascular death: log-rank 29.1, p <0.001) and female patients (all-cause death: log-rank 14.2, p 0.00134; cardiovascular death: log-rank 7.2, p 0.027)¼. Additionally, the spline curves in the whole population as well as in men and women showed a progressive improvement in prognosis up to 25 kg/m² BMI (Supplemental Figures 3 and 4).

In the prognostic model including age, gender, ischaemic aetiology, eGFR, LVEF, NYHA I–II vs.
Table 1. Population characteristics.

<table>
<thead>
<tr>
<th>Population characteristic</th>
<th>All</th>
<th>BMI categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 6468</td>
<td>N = 2221 (34%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>68 (58–76)</td>
<td>72 (64–79)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>5071 (78)</td>
<td>38 (42)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.6 (23.8–29.9)</td>
<td>17.4 (16.6–18.0)</td>
</tr>
<tr>
<td>Ischaemic aetiology, n (%)</td>
<td>3650 (76)</td>
<td>45 (50)</td>
</tr>
<tr>
<td>NYHA I–II/III–IV, n (%)</td>
<td>3715/2381 (57/37)</td>
<td>36/45 (40/50)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2905 (45)</td>
<td>35 (39)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1721 (27)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>AF, n (%)</td>
<td>1056 (16)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>864 (13)</td>
<td>24 (27)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>27 (21–34)</td>
<td>26 (21–32)</td>
</tr>
<tr>
<td>LVEF &lt;40%, 40–49%, c50%, n (%)</td>
<td>5848, 411, 172</td>
<td>78, 6, 5</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>46 (1.8–9.8)</td>
<td>4.6 (1.1–8.3)</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>2336 (956–4956)</td>
<td>2336 (1254–8368)</td>
</tr>
<tr>
<td>hs-TnT, ng/L</td>
<td>18 (9–33)</td>
<td>18 (13–34)</td>
</tr>
<tr>
<td>sST2, ng/mL</td>
<td>27 (20–39)</td>
<td>31 (22–36)</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>5722 (89)</td>
<td>73 (81)</td>
</tr>
<tr>
<td>BB, n (%)</td>
<td>3128 (48)</td>
<td>37 (41)</td>
</tr>
<tr>
<td>MRA, n (%)</td>
<td>1113 (17)</td>
<td>23 (26)</td>
</tr>
</tbody>
</table>

Significant p values are reported in bold.
ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF: atrial fibrillation; BB: beta-blocker; BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein; hs-TnT: high-sensitivity troponin T; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonists; NT-proBNP: N-terminal fraction of pro-B-type natriuretic peptide; NYHA: New York Heart Association; sST2: soluble suppression of tumorigenesis-2.
Figure 1. Per cent body fat and patient survival. Per cent body fat is estimated based on the Jackson–Pollock formula. Patients (Pts) are stratified according to tertiles of per cent body fat. When using the Gallagher formula, the log-rank values for all-cause death and cardiovascular (CV) death were 13.3 ($p = 0.001$), and 8.1 ($p = 0.017$).

Figure 2. Per cent body fat and prognosis: spline curve analysis. Spline curve analysis. Per cent body fat is calculated using the Jackson–Pollock equation. The inflection points of the curves are: 27.9% (all-cause death) and 27.6% (cardiovascular (CV) death). When using the Gallagher equation, the inflection points of the curves for all-cause death are 26.2 and 26.6%, respectively. HR: hazard ratio

III–IV, hypertension, COPD, diabetes, atrial fibrillation, hs-CRP, ACEi/ARB, beta blockers and MRA therapy, patients with BMI 25 kg/m$^2$ cut-off had a better prognosis for all-cause death (hazard ratio 0.74, 95% confidence interval (CI) 0.66–0.84; $p < 0.001$) and cardiovascular death (hazard ratio 0.80, 95% CI 0.70–0.91; $p = 0.001$).

**PBF: estimates and prognostic value**

Median PBF was 26.9% (22.4–33.0%) with the Jackson–Pollock equation, and 28.0% (23.8–33.5%) with the Gallagher equation, with an extremely strong correlation ($r = 0.96$, $p < 0.001$). Patient characteristics across PBF tertiles are provided in Supplemental
Table 2. Percent body fat (PBF) as predictor of outcome.

<table>
<thead>
<tr>
<th>All-cause death</th>
<th>Cardiovascular death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doubling of PBF</td>
<td>I&lt;sub&gt;1&lt;/sub&gt; vs. 2&lt;sup&gt;nd&lt;/sup&gt;3&lt;sup&gt;rd&lt;/sup&gt; tertiles</td>
</tr>
<tr>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>------</td>
<td>--------</td>
</tr>
<tr>
<td>Jackson-Pollock</td>
<td>0.68</td>
</tr>
<tr>
<td>Gallagher</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>0.85</td>
</tr>
</tbody>
</table>

The risk is calculated per each doubling of PBF (by considering log<sub>2</sub>-transformed variables) or the first vs. the second and third tertiles (Jackson-Pollock equation: <23.9% vs. ≥23.9%; Gallagher equation: <25.1% vs. ≥25.1%).

The model for multivariate analysis includes age, gender, ischaemic aetiology, estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class I-II vs. III-IV, hypertension, chronic obstructive pulmonary disease (COPD), diabetes, atrial fibrillation, hs-C-reactive protein (hs-CRP), therapy with angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (ACEi/ARB), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA).

CI: confidence interval; HR: hazard ratio.

Table 2. Patients in the first PBF tertile had the worst prognosis, while patients in the second and third tertiles had similar survival (Figure 1). The improvement in patient prognosis with increasing PBF, in the whole population and in both genders, was visually represented by spline curves (Figure 2 and Supplemental Figure 5).

In the prognostic model above, PBF independently predicted all-cause and cardiovascular mortality. In detail, the risks of all-cause and cardiovascular death decreased by up to 36% and 27%, respectively, per each doubling of PBF (Table 2). Furthermore, prognosis was better in the second or third tertiles than in the first tertile regardless of model variables (Table 2). In both cases (i.e. considering absolute PBF values or first tertile vs. second or third tertile) metrics of risk reclassification were improved (Supplemental Table 3).

Plasma NT-proBNP, hs-TnT and sST2 according to BMI and PBF

As stated above, the decrease in NT-proBNP with increasing BMI category was much more prominent than variations observed in either hs-TnT or sST2, despite significant differences for all three biomarkers (Figure 3). Accordingly, though weak, the correlation between BMI and NT-proBNP was stronger (r 0.257) than the correlation with either hs-TnT (r 0.057) or sST2 (r 0.107; all p <0.001). In multivariate linear regression analysis, when considering the same model used for prognostic assessment, BMI independently predicted both NT-proBNP and sST2, but not hs-TnT (Supplemental Table 4). Similar results were found for PBF (Supplemental Tables 2 and 4).

The three biomarkers were then added to the prognostic model above. In the obese subgroup (BMI 30 kg/m<sup>2</sup>) and in the third PBF tertile, NT-proBNP was not an independent predictor of outcome, in contrast to both hs-TnT and sST2. This pattern was not observed across the other BMI or PBF categories (Table 3 and Supplemental Table 5).

Discussion

This analysis, performed in a large individual heart failure patient dataset designed to assess the prognostic value of biomarkers, confirms that overweight and obese heart failure patients have longer survival, and provides the first demonstration of a direct relationship between body fat content and better outcome. We also report that obesity influences NT-proBNP considerably more than hs-TnT and sST2, and NT-proBNP appeared less prognostic in a model including hs-TnT or sST2 among obese patients.

The better prognosis of obese heart failure patients is so counterintuitive that it has been attributed to limitations of BMI as a synthetic anthropometric measure. To verify this hypothesis, sophisticated evaluations of body composition such as bioelectrical impedance analysis should be performed. Unfortunately, large datasets of heart failure patients with these measures are not available, and even a very simple index such as the WHR has been assessed only in a single cohort of limited size (n=479), including patients with either acute or chronic heart failure. One may also consider the WHR to be a measure reflecting both subcutaneous and visceral abdominal fat, also influenced by hip size (so that WHR should preferably be measured together with waist circumference). In the search for measures more closely correlated to body composition than BMI, more accurate than WHR, and potentially available from large population datasets, we estimated the percentage of body weight composed of fat tissue. We used two equations introduced and validated against direct measurements of body compositions. These estimates of
Figure 3. Circulating biomarkers across categories of body mass index (BMI) and per cent body fat (PBF) tertiles. All p values are <0.001. PBF is calculated through the Jackson–Pollock equation (first tertile: <23.9%; second tertile: 23.9-30.5%; third tertile: ≥30.5%).

hs-TnT: high-sensitivity troponin T; NT-proBNP: N-terminal fraction of pro-B-type natriuretic peptide; sST2: soluble suppression of tumorigenesis-2

PBF displayed a very strong correlation (r=0.996). A higher PBF was consistently associated with lower all-cause and cardiovascular mortality. Accordingly, spline curves showed a progressive improvement in prognosis up to a PBF around 27%, beyond which patient prognosis remained basically stable. Both PBF (modelled continuously) and the first versus second or third PBF tertiles were independent
predictors of outcome and improved metrics of risk reclassification in a model including several baseline variables with prognostic significance (age, gender, ischaemic aetiology, eGFR, LVEF, NYHA class, several comorbidities, hs-CRP and medical therapy).

To the best of our knowledge, we are the first to assess PBF in patients with heart failure, and to report that patients with higher PBF have lower all-cause and cardiovascular mortality, as well as lower NT-proBNP, but not hs-TnT or sST2, levels. While assessing this point was the main goal of our analysis, these results deserve considerations also from the perspective of prognostic stratification. Most notably, we observed that patients with BMI 25 kg/m² had a 26% lower risk of all-cause mortality, and a 20% lower risk of cardiovascular mortality, regardless of other baseline variables. Similarly, patient prognosis was better in the second or third PBF tertiles than in the first tertile. A simple and widely used measure such as the BMI, and possibly also PBF estimates through simple equations, should then be considered for the prediction of fatal endpoints in heart failure outpatients.

With regard to NT-proBNP, hs-TnT and sST2, which rank among the strongest predictors of outcome in heart failure,14,15 the influence of BMI or PBF was much more prominent for NT-proBNP than for sST2 and hs-TnT, as demonstrated through correlation and multivariate linear regression analyses. Interestingly, the three biomarkers were independent predictor of outcome in all BMI categories and PBF tertiles, except for obese patients (BMI 30 kg/m²) or the high-PBF tertile, where only hs-TnT and sST2 remained independent predictors of all-cause and cardiovascular mortality, arguably establishing these biomarkers as the tests of choice for refined prognostication in obese patients with heart failure.

**Study limitations and perspectives for future studies**

Some limitations of this hypothesis-generating study must be acknowledged. First, although our results provide a quite compelling demonstration of the link between higher PBF and longer survival in heart failure, it is important to notice that PBF was estimated through equations developed and validated in healthy subjects. These results should then be verified in prospective studies using direct measurements of body composition or anthropometric measures, as in prior studies.28–30 Second, the number of underweight individuals was low, possibly because underweight heart failure patients often have cardiac cachexia or advanced, life-limiting disorders, and such patients were not enrolled in clinical trials; because of the poor prognosis of these underweight patients, their inclusion in the analysis would have further strengthened the proposed relationship between BMI or PBF and outcome. Third, our dataset did not allow to assess the nutritional status of these patients, which might hold prognostic significance,31 and did not include many variables related to metabolic disturbances and cardiovascular risk (such as lipid profile, liver steatosis, alcohol intake or exercise) or echocardiographic parameters (for example, indices of diastolic function or hypertrophy patterns). Fourth, no information was available regarding the changes in weight, BMI or PBF over time, although the temporal trends of these parameters might hold prognostic significance. Future studies exploring these aspects are warranted.

**Conclusions**

In parallel with increasing BMI or PBF there is an improvement in patient prognosis and a decrease in NT-proBNP, but not hs-TnT or sST2. hs-TnT or sST2 are stronger predictors of outcome than NT-proBNP among obese patients.

**Author contribution**

Study design: AA, MEm, CP. Data analysis: AA, AR. Critical revision: AA, JLJ, AC, RL, JM, ISA, JNC, JG, TU, SHN, HPBLR, ABG, JL, RADB, Ay, YT, MEG, IG, HKG, KME, KH, IT.

**Declaration of conflicting interests**

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