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RESEARCH ARTICLE

Clinical effect of obesity on N-terminal pro-B-type natriuretic peptide cut-off concentrations for the diagnosis of acute heart failure

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Aims Obese patients have lower natriuretic peptide concentrations. We hypothesized that adjusting the concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for obesity could further increase its clinical utility in the early diagnosis of acute heart failure (AHF).

Methods and results This hypothesis was tested in a prospective diagnostic study enrolling unselected patients presenting to the emergency department with acute dyspnoea. Two independent cardiologists/internists centrally adjudicated the final diagnosis using all individual patient information including cardiac imaging. NT-proBNP plasma concentrations were applied: first, using currently recommended cut-offs; second, using cut-offs lowered by 33% with body mass index (BMI) of 30–34.9 kg/m^2 and by 50% with BMI $\geq$ 35 kg/m^2. Among 2038 patients, 509 (25%) were obese, of which 271 (53%) had AHF. The diagnostic accuracy of NT-proBNP as quantified by the area under the receiver-operating characteristic curve was lower in obese versus non-obese patients (0.890 vs. 0.938). For rapid AHF rule-out in obese patients, the currently recommended cut-off of 300 pg/ml achieved a sensitivity of 96.7% (95% confidence interval [CI] 93.8–98.2%), ruling out 29% of patients and missing 9 AHF patients. For rapid AHF rule-in, the age-dependent cut-off concentrations (age <50 years: 450 pg/ml; age 50–75 years: 900 pg/ml; age >75 years: 1800 pg/ml) achieved a specificity of 84.9% (95% CI 79.8–88.9%). Proportionally lowering the currently recommended cut-offs by BMI increased sensitivity to 98.2% (95% CI 95.8–99.2%), missing 5 AHF patients; reduced the proportion of AHF patients remaining in the 'gray zone' (48% vs. 26%; $p = 0.002$), achieving a specificity of 76.5% (95% CI 70.7–81.4%).

Conclusions Adjusting NT-proBNP concentrations for obesity seems to further increase its clinical utility in the early diagnosis of AHF.

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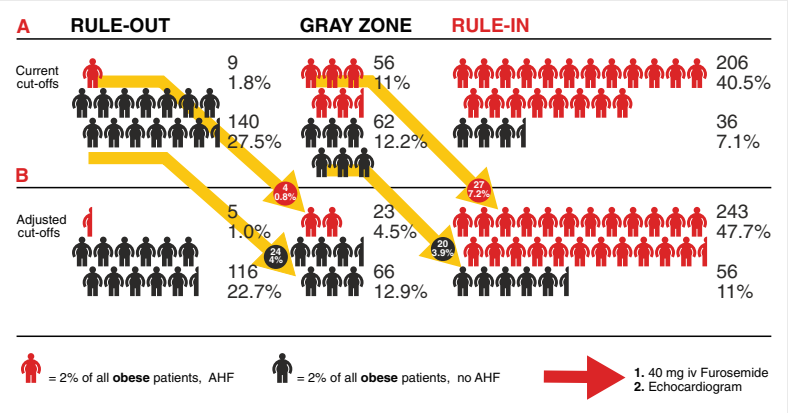
Graphical Abstract



Obese patients ruled out and ruled in or remaining in the 'gray zone' after: (*A*) applying the currently recommended N-terminal pro-B-type natriuretic peptide cut-offs, or (*B*) reducing these cut-offs by one third in patients with a body mass index 30–34.9 kg/m^2 and by half in those with a body mass index ≥35 kg/m^2. Red figures represent patients with acute heart failure (AHF) and black figures show patients without AHF as a final diagnosis. One full figure represents 2% of all obese patients. Golden arrows indicate the number (and %) of reclassified patients. For instance, when applying the reduced cut-offs, 37 AHF patients (7.2% of the overall patient population) in the 'gray zone' were ruled in with their correct diagnosis. The red arrow represents the most common immediate consequences of 'rule-in' of AHF in the emergency department; specifically, bolus of 40 mg intravenous furosemide and ordering an echocardiogram.

Keywords Acute heart failure • Diagnosis • Natriuretic peptides • Obesity • Cut-offs

Introduction

Acute heart failure (AHF) is the most common diagnosis in the emergency department (ED) leading to hospitalization and is still associated with an unacceptably high morbidity and mortality.[1,2] AHF patients' dismal outcome may be at least partly due to diagnostic uncertainty in the ED and the associated delay in diagnosis and effective treatment initiation.[2]

Natriuretic peptides are quantitative plasma biomarkers for the presence and severity of haemodynamic cardiac stress and heart failure, and their use has substantially improved the rapid detection of AHF among patients presenting with acute dyspnoea.[3–6] Accordingly, natriuretic peptides' diagnostic use has received a class I recommendation in clinical practice guidelines.[1] Obese patients, both with and without AHF, seem to have lower B-type natriuretic peptide (BNP) concentrations.[7–10] The clinical implications of the association of obesity and natriuretic peptides are reasonably well defined for BNP. Based on data from a large diagnostic study, lower cut-offs are recommended in obesity to not miss patients with mild AHF.[6,11] In contrast, the clinical implications are less well defined for N-terminal pro-B-type natriuretic peptide (NT-proBNP).[1,6,12]

We aimed to address this major gap in knowledge by evaluating the impact of obesity on the diagnostic performance of currently recommended NT-proBNP cut-offs in the diagnosis of AHF and, if necessary, derive novel cut-offs for obese patients in a large multicentre diagnostic study.

Methods

Study population and design

Basics in Acute Shortness of Breath EvaLuation (BASEL V, NCT01831115) was a prospective, multicentre diagnostic study aimed at advancing the early detection and management of patients with AHF.[13] Adult patients presenting to the ED of two Swiss University Hospitals (Basel and Zurich) with chief complaint of acute dyspnoea were enrolled. While enrolment was independent of renal function, patients with end-stage kidney failure on chronic dialysis were excluded. For this analysis, patients were also excluded if they did not have documented body mass index (BMI) or NT-proBNP measured at ED presentation, if the final diagnosis remained unclear even after central adjudication, and if patients were adjudicated as having cardiac dyspnoea due to acute coronary syndrome or arrhythmia without any other evidence of AHF.

The study was conducted following the principles of the Declaration of Helsinki and approved by the local ethics committees. All patients provided informed consent. The authors designed the study, collected and analysed the data using the STARD guidelines (online supplementary *Table S1*), vouch for the data and analysis, wrote the paper, and decided to submit for publication.

Final diagnosis adjudication

Two independent cardiologists/internists adjudicated the final diagnosis using all available clinical information including clinical history, physical

examination, 12-lead electrocardiogram, laboratory findings including BNP (in 80%) or NT-proBNP (in 20%), chest X-ray, echocardiography, lung function testing, computed tomography, response to therapy, and autopsy data for patients who died in hospital.[1,14,15] Including BNP/NT-proBNP in the final adjudication was necessary to maximize the accuracy of the final diagnosis adjudication. In situations of disagreement, cases were reviewed and adjudicated in conjunction with a third cardiologist.

Outcome measures

Specificity, positive predictive value (PPV), and percentage of obese patients triaged towards rule in for AHF were the primary outcome measures for the age-dependent NT-proBNP rule-in cut-offs (450 ng/L if <50 years, 900 ng/L if 50–75 years, and 1800 ng/L if >75 years).[1] Sensitivity, negative predictive value (NPV), and percentage of obese patients triaged towards rule out were the primary outcome measures for the universal NT-proBNP rule-out cut-off (300 ng/L).[1] Secondary outcome measures included: (i) percentage of obese patients remaining in the 'gray zone' (not triaged towards either rule out or rule in by currently recommended cut-offs); (ii) NT-proBNP diagnostic accuracy for obese patients as quantified by the area under the receiver-operating characteristic curve (AUC), and (iii) the value of a previously proposed reduction of up to 50% for the currently recommended cut-off levels for obese patients.[6] Specifically, in patients with BMI of 30–34.9 kg/m^2, currently recommended cut-offs were reduced by 33% and by 50% for those with BMI ≥35 kg/m^2. In a sensitivity analysis, cut-offs were reduced by 33% or by 50% for all obese patients (online supplementary *Methods*).

Statistical methods

Kolmogorov–Smirnov test was used for testing normality. Continuous variables were presented as medians (with interquartile range [IQR]) and categorical variables as numbers and percentages. Comparisons between groups were made using Chi-square, Mann–Whitney U test or Kruskal–Wallis test, as appropriate. Differences in independent proportions were assessed using two-sample test for equality of proportions. Confidence intervals (CIs) for the difference between independent proportions were computed according to Miettinen and Nurminen.[16–18]

Sensitivity, specificity, NPV as well as PPV were calculated for the respective NT-proBNP diagnostic cut-offs. Safety was assessed as the sensitivity and NPV of ruling out AHF. Accuracy was evaluated as the specificity and PPV of ruling in AHF. Sensitivity and specificity were compared using McNemar test for paired proportions.[19] To compare different cut-offs' NPV and PPV, a weighted generalized score statistic was used.[20] CIs of proportions were computed using Wilson's method.[21] Cut-off efficacy was evaluated by determining number of patients remaining in the NT-proBNP diagnostic 'gray zone' as a proportion of the total study population as well as number of patients with AHF as a proportion of the number of patients remaining in the 'gray zone', with comparison by McNemar test for paired proportions. NT-proBNP diagnostic accuracy to diagnose AHF was quantified using AUC. AUC CIs and *p*-values for their comparison were calculated according to DeLong *et al.*[22]

We assessed improvement in algorithm performance for reduction in NT-proBNP cut-off values by calculating difference in diagnostic accuracy, net reclassification improvement (NRI) and net benefit as recommended by the TRIPOD statement (online supplementary *Methods*).[23]

To demonstrate lack of inclusion bias, sensitivity analysis was performed after exclusion of patients in whom NT-proBNP was available for the final adjudication. All hypothesis testing was two-sided and a *p*-value <0.05 was regarded as statistically significant. Statistical analyses were carried out with SPSS/PC (version 25.0) and R (version 3.6.3).

Results

Patient demographics and characteristics

Enrolled between April 2006 and February 2014, 2038 patients were eligible for this analysis (online supplementary *Figure S1*). Median BMI was 25.9 (22.5–30) kg/m^2, median age was 75 (62–82), and 897 (44%) of patients were women (online supplementary *Table S2*). AHF was the adjudicated final diagnosis in 1034 (51%) patients. Among the non-AHF patients, obstructive pulmonary disease and pneumonia were the most common causes of acute dyspnoea (online supplementary *Table S3*). The baseline characteristics of obese versus non-obese patients who did not receive the final diagnosis of AHF are presented in online supplementary *Table S4*.

Obesity, acute heart failure prevalence, and NT-proBNP concentrations

Among 509 (25%) obese patients, 271 (53%) had an adjudicated final diagnosis of AHF. There was no statistically significant difference between the AHF prevalence in obese and non-obese patients ($p = 0.192$; *Table 1*). NT-proBNP concentrations were significantly lower in obese versus non-obese patients (*Table 2*). For instance, median NT-proBNP concentrations in obese patients with AHF were roughly one-third lower compared to non-obese AHF patients (1029 [IQR 198–3558] ng/L vs. 1521 [IQR 244–6072] ng/L; $p < 0.001$). Among obese patients, BMI ≥35 kg/m^2 was associated with further decrease in NT-proBNP concentrations (online supplementary *Table S5*). The distribution of ejection fraction groups, AHF and their impact on NT-proBNP concentrations in obese and non-obese patients are addressed in online supplementary *Results* and *Tables S6* and *S7*.

Diagnostic performance of currently recommended NT-proBNP cut-off concentrations in obese versus non-obese patients

NT-proBNP diagnostic accuracy for AHF as quantified by the AUC was lower in obese (0.890; 95% CI 0.861–0.920) versus non-obese patients (0.938; 95% CI 0.927–0.950; $p = 0.003$; *Figure 1*). Using a uniform cut-off of 300 ng/L in obese patients to exclude the diagnosis of AHF resulted in a lower sensitivity (96.7%; 95% CI 93.8–98.2%) and NPV (94.0%; 95% CI 88.9–96.8%) versus non-obese (sensitivity 98.7%; 95% CI 97.6–99.3%; NPV 97.7%; 95% CI 95.8–98.8%; difference in sensitivity −2.0%; 95% CI -3.7%

Table 1 Baseline demographics, medical history, symptoms and signs, results of physical examination, laboratory testing, and transthoracic echocardiography in obese and non-obese patients

Characteristics	Obese patients (n = 509)	Non-obese patients (n = 1529)	p-value
Age, years, median (IQR)	70 (59–78)	76 (63–83)	<0.001
Female sex, *n* (%)	216 (42)	681 (45)	0.408
AHF, *n* (%)	271 (53)	763 (50)	0.192
LVEF[a], %, median (IQR)	53 (40–60)	55 (38–60)	0.244
NT-proBNP, ng/L, median (IQR)	1029 (198–3558)	1521 (244–6072)	<0.001
eGFR[b], ml/min/1.73 m^2, median (IQR)	68 (44–88)	69 (44–89)	0.780
Prior history, *n* (%)			
Prior AHF	177 (35)	469 (31)	0.100
Hypertensive heart disease	140 (28)	313 (21)	0.002
Coronary artery disease	176 (35)	497 (33)	0.430
Prior myocardial infarction	89 (18)	289 (19)	0.495
Hypertension	402 (79)	965 (63)	<0.001
Atrial fibrillation	136 (27)	410 (27)	0.898
Diabetes mellitus	198 (39)	267 (18)	<0.001
COPD	166 (33)	512 (34)	0.691
Tobacco use (past or present)	338 (68)	983 (67)	0.527
Medication at admission, *n* (%)			
ACE inhibitors	164 (33)	465 (31)	0.358
ARBs	136 (28)	250 (17)	<0.001
Beta-blockers	264 (53)	602 (40)	<0.001
Aldosterone antagonists	48 (9.7)	117 (7.7)	0.175
Diuretics	303 (61)	724 (48)	<0.001
Symptoms/signs, *n* (%)			
PND	198 (41)	567 (39)	0.573
Orthopnoea	261 (53)	692 (48)	0.027
Chest pain	205 (41)	558 (37)	0.121
Cough	285 (57)	932 (63)	0.036
Fever	82 (16)	262 (18)	0.556
Sputum production	206 (41)	644 (43)	0.475
Physical examination, *n* (%)			
Jugular venous distension	90 (22)	374 (26)	0.062
Rales on lung exam	217 (44)	676 (46)	0.484
Wheezing on lung exam	137 (28)	342 (23)	0.034
S3 gallop	1 (0.3)	19 (2.0)	0.027
Lower extremity oedema	288 (58)	546 (36)	<0.001
ECG findings, *n* (%)			
Atrial fibrillation	110 (22)	337 (22)	0.839
LBBB	33 (6.5)	121 (8.4)	0.290
Chest radiography findings, *n* (%)			
Interstitial oedema	77 (15)	213 (14)	0.503
Pleural effusion	131 (26)	452 (30)	0.098
Infiltrate/pneumonia	71 (14)	247 (16)	0.235
Cardiomegaly	203 (40)	510 (33)	0.007
Cephalization of vessels	157 (31)	373 (24)	0.004

ACE, angiotensin-converting enzyme; AHF, acute heart failure; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PND, paroxysmal nocturnal dyspnoea.

[a]Information on LVEF was available in 1039 (51%) of all patients and in 283 (56%) of the obese patients at the time of presentation to the emergency department with dyspnoea.

[b]Calculated by using the Chronic Kidney Disease Epidemiology Collaboration formula. Information on eGFR was available in 1758 (86%) of all patients and in 441 (87%) of the obese patients at the time of presentation to the emergency department with dyspnoea.

Table 2 **N-terminal pro-B-type natriuretic peptide plasma concentrations in obese and non-obese patients**

	Overall	Obese patients	Non-obese patients	*p*-value
All patients, *n* (%)	2038 (100)	509 (25)	1529 (75)	
NT-proBNP, pg/ml, median (IQR)	1334 (230–5180)	1029 (198–3558)	1521 (244–6072)	<0.001
AHF, *n* (%)	1034 (51)	271 (13)	763 (37)	
NT-proBNP, pg/ml, median (IQR)	4735 (2014–9739)	2884 (1162–5869)	5629 (2339–11 471)	<0.001
Non-AHF, *n* (%)	1004 (49)	238 (12)	766 (38)	
NT-proBNP, pg/ml, median (IQR)	236 (75–712)	193 (59–612)	250 (80–764)	0.051

AHF, acute heart failure; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

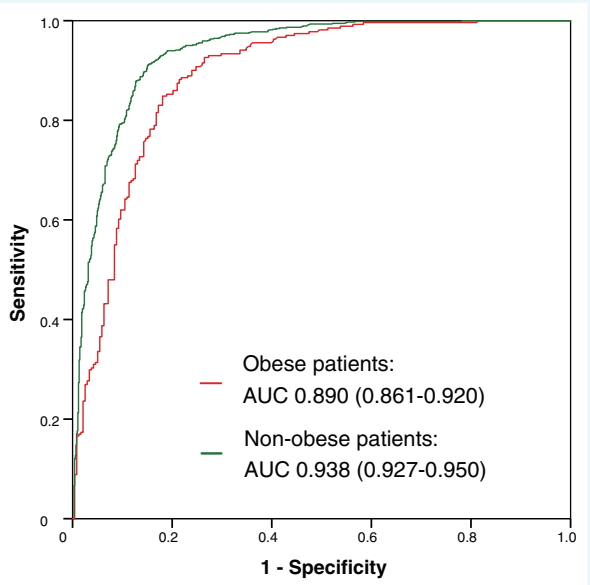


Figure 1 Receiver-operating characteristic curves describing the diagnostic performance of N-terminal pro-B-type natriuretic peptide in obese and non-obese patients. AUC, area under the curve.

to −0.3%; $p = 0.003$; difference in NPV −3.7%; 95% CI −5.9% to −1.5%; $p < 0.001$; *Table 3*). When using currently recommended age-dependent rule-in cut-offs (450 ng/L if age <50 years; 900 ng/L if 50–75 years, and 1800 ng/L if age >75 years) to confirm the AHF diagnosis, in obese patients specificity (84.9%; 95% CI 79.8–88.9%) and PPV (85.1%; 95% CI 80.1–89.1%) were similar to those of non-obese patients (specificity 84.1%; 95% CI 81.3–86.5%; PPV 84.4%; 95% CI 81.7–86.8%; difference in specificity 0.8%; 95% CI −2.8% to 4.4%; $p = 0.667$; difference in PPV 0.7%; 95% CI −2.9% to 4.3%; $p = 0.705$).

The proportion of patients remaining in the 'gray zone' was 21% overall (428 patients), and of these, 118 patients (29%) were obese (*Figure 2*). In the 'gray zone' of currently recommended NT-proBNP cut-offs, there were statistically significant more AHF patients with obesity when compared to non-obese patients (56 [48%] vs. 94 [30%]; $p < 0.001$; online supplementary *Table S8*).

Diagnostic performance of currently recommended and reduced NT-proBNP cut-off concentrations in obese patients

In obese patients, the currently recommended rule-out cut-off (<300 ng/L) ruled out 149 patients (29%), missing 9 (3.3%) of 271 patients with AHF. Patients' baseline characteristics are presented in online supplementary *Table S9*. After reducing the currently recommended rule-out cut-off by 33% for patients with BMI of 30.0–34.9 kg/m^2 and by 50% for patients with BMI ≥35.0 kg/m^2, the proposed cut-offs ruled out 121 patients (24%), with 98.2% (95% CI 95.8–99.2%) sensitivity and 95.9% (95% CI 90.7–98.2%) NPV, missing 5 (1.8%) of 271 AHF patients (online supplementary *Table S10*). In comparison, the sensitivity of the proposed new rule-out cut-offs was higher than for currently recommended cut-offs (difference for sensitivity of 1.5%; 95% CI 0.04–2.9%; $p = 0.045$; difference for NPV of 1.9%; 95% CI −0.4% to 4.8%; $p = 0.181$).

Overall, in obese patients, currently recommended age-dependent rule-in cut-offs ruled in 242 patients (48%), of which 206 had AHF. After reducing currently recommended rule-in cut-offs by 33% in patients with BMI of 30.0–34.9 kg/m^2 and by 50% in patients with BMI ≥35.0 kg/m^2, the proposed cut-offs ruled in 299 patients (59%), with 76.5% (95% CI 70.7–81.4%) specificity and PPV of 81.3% (95% CI 76.5–85.3%). Of them, 243 had AHF. In comparison, both specificity and PPV of the proposed new rule-in cut-offs were lower than for currently recommended cut-offs (difference for specificity −8.4%; 95% CI −11.9% to −4.9%; $p < 0.001$; difference for PPV −3.9%; 95% CI −6.5% to −1.2%; $p = 0.007$).

Proportionally reducing currently recommended cut-offs by 33% for patients with BMI 30–34.9 kg/m^2 and by 50% for BMI ≥35 kg/m^2 led to a significant reduction of patients remaining in the 'gray zone' (118 [23%] vs. 89 [17%] patients with modified cut-offs; *Graphical Abstract*) with smaller proportion of AHF patients (56 [48%] vs. 23 [26%] patients with modified cut-offs; $p = 0.002$; *Figure 2*). Furthermore, when comparing obese versus non-obese AHF patients, there was no longer any significant difference between the proportion of AHF patients remaining in the 'gray zone' (23 [26%] vs. 94 [30%]; $p = 0.413$; online supplementary *Table S11*).

When accounting for relative weighting (harm-to-benefit ratio) of 1:2 for false positive decisions (ruling in a patient without having AHF; as these patients would easily be identified by echocardiography, the mandatory next step after rule in of AHF by NT-proBNP) versus true positive decisions (ruling in a patient with AHF), the

Table 3 Diagnostic performance of the currently recommended N-terminal pro-B-type natriuretic peptide cut-off concentrations for the diagnosis or exclusion of acute heart failure in obese and non-obese patients

		Recommended cut-off concentration	Sensitivity, % (95% CI)	NPV, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)
Exclusionary ('rule-out') cut-off concentration						
All age groups	Overall (n = 2038)	300 ng/L	98.2 (97.1–98.8)	96.8 (95–97.9)	56.6 (53.5–59.6)	70.0 (67.5–72.3)
	Obese patients (n = 509)		96.7 (93.8–98.2)	94.0 (88.9–96.8)	58.8 (52.5–64.9)	72.8 (68–77.1)
	Non-obese patients (n = 1529)		98.7 (97.6–99.3)	97.7 (95.8–98.8)	55.9 (52.3–59.4)	69.0 (66.2–71.7)
Confirmatory ('rule-in') cut-off concentrations						
All age groups	Overall (n = 2038)	Age-dependent	83.7 (81.3–85.8)	83.3 (80.9–85.5)	84.3 (81.9–86.4)	84.6 (82.2–86.6)
	Obese patients (n = 509)		76.0 (70.6–80.7)	75.7 (70.2–80.4)	84.9 (79.8–88.9)	85.1 (80.1–89.1)
	Non-obese patients (n = 1529)		86.4 (83.8–88.6)	86.1 (83.4–88.4)	84.1 (81.3–86.5)	84.4 (81.7–86.8)
Confirmatory ('rule-in') cut-off concentrations						
Age <50 years	Overall (n = 222)	450 ng/L	89.3 (72.8–96.3)	98.3 (95.2–99.4)	91.2 (86.4–94.5)	59.5 (44.5–73)
	Obese patients (n = 62)		87.5 (64–96.5)	95.7 (85.5–98.8)	95.7 (85.5–98.8)	87.5 (64–96.5)
	Non-obese patients (n = 160)		91.7 (64.6–98.5)	99.3 (95.9–99.9)	89.9 (84–93.8)	42.3 (25.5–61.1)
Age 50–75 years	Overall (n = 838)	900 ng/L	88.6 (84.7–91.6)	91.8 (88.9–93.9)	84.0 (80.5–86.9)	78.5 (74.0–82.3)
	Obese patients (n = 271)		83.3 (76.1–88.7)	83.9 (76.9–89.1)	82.7 (75.6–88.1)	82.1 (74.7–87.7)
	Non-obese patients (n = 567)		92.0 (87.5–95)	95.1 (92.2–96.9)	84.4 (80.4–87.8)	76.4 (70.7–81.4)
Age >75 years	Overall (n = 978)	1800 ng/L	81.0 (77.8–83.8)	65.7 (60.7–70.3)	80.3 (75.5–84.4)	90.1 (87.4–92.2)
	Obese patients (n = 176)		66.7 (57.9–74.4)	51.2 (40.7–61.6)	81.1 (68.6–89.4)	89.1 (81.1–94.0)
	Non-obese patients (n = 802)		84.2 (80.9–87)	69.9 (64.4–74.9)	80.2 (74.8–84.6)	90.3 (87.4–92.5)

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

net benefit increase for the conventional cut-offs was 0.369, being 0.422 for the proposed new cut-offs, resulting in a net benefit of the proposed cut-offs with respect to the old cut-offs of 5.3%. This triage strategy using the proposed reduced NT-proBNP cut-offs would be expected to lead to 53 more patients with AHF correctly ruled in (true positives) per 1000 patients at the same number of non-AHF patients being incorrectly ruled in (false positives; online supplementary *Table S12*).

Sensitivity analysis

Results of reducing the NT-proBNP cut-offs by 33% or by 50% in all obese patients are presented in online supplementary *Tables S12–S19* and *Figures S2–S5*. These cut-offs' sensitivity, NPV, specificity and PPV were comparable (online supplementary *Tables S13* and *S14*). The proportion of patients remaining in the 'gray zone' was also comparable (online supplementary *Tables S15* and *S16*). The net benefit achieved by reducing the cut-offs for obese patients by 33% (3.43%) or by 50% (4.81%) was lower than the one of the combined strategy (5.30%; online supplementary *Table S12*).

Table 4 summarizes the sensitivity, NPV, specificity, and PPV of the different cut-offs applied for the exclusion or diagnosis of AHF. This overview may mandate a strategy where only the rule-out cut-off is reduced to increase the sensitivity and to keep the currently recommended rule-in cut-off plasma concentrations unchanged. This would simultaneously allow to retain their high specificity and PPV (online supplementary *Table S20*). Nevertheless, this strategy will leave a higher proportion of patients in the NT-proBNP diagnostic uncertainty 'gray zone'. Thereby, as compared to the strategy of adjusting both rule-in and rule-out cut-off concentrations, also the number of AHF patients remaining in the 'gray zone' will be larger (online supplementary *Table S21*).

Additional sensitivity analyses are presented in online supplementary *Results* and *Tables S22–S30*.

Discussion

This analysis within a large prospective diagnostic study addressed a major gap in knowledge: detailed quantification of obesity impact on currently recommended NT-proBNP cut-offs in the diagnosis of AHF.[1] We report seven major findings. First, the study confirms that beyond AHF presence or absence, BMI had a substantial impact on NT-proBNP plasma concentrations.[6,7,24,25] For instance, among AHF patients, the obese had roughly half the NT-proBNP levels of the non-obese. Notably, obese patients were younger, which may partly explain their lower NT-proBNP levels. Second, AHF prevalence did not significantly differ among pre-defined BMI groups. Notably, the sample sizes per BMI category were not very large; thus, the lack of a significant difference in AHF prevalence in the BMI groups might be due to lack of statistical power. From a clinical perspective, obesity may exacerbate dyspnoea and, together with the association with higher prevalence of cardiovascular risk factors, guide the clinician choice toward AHF even in the presence of lower NT-proBNP concentrations. Third, this study confirms that as a continuous variable in the diagnosis of AHF, NT-proBNP provided higher diagnostic accuracy in non-obese versus obese patients, reflecting the increasing

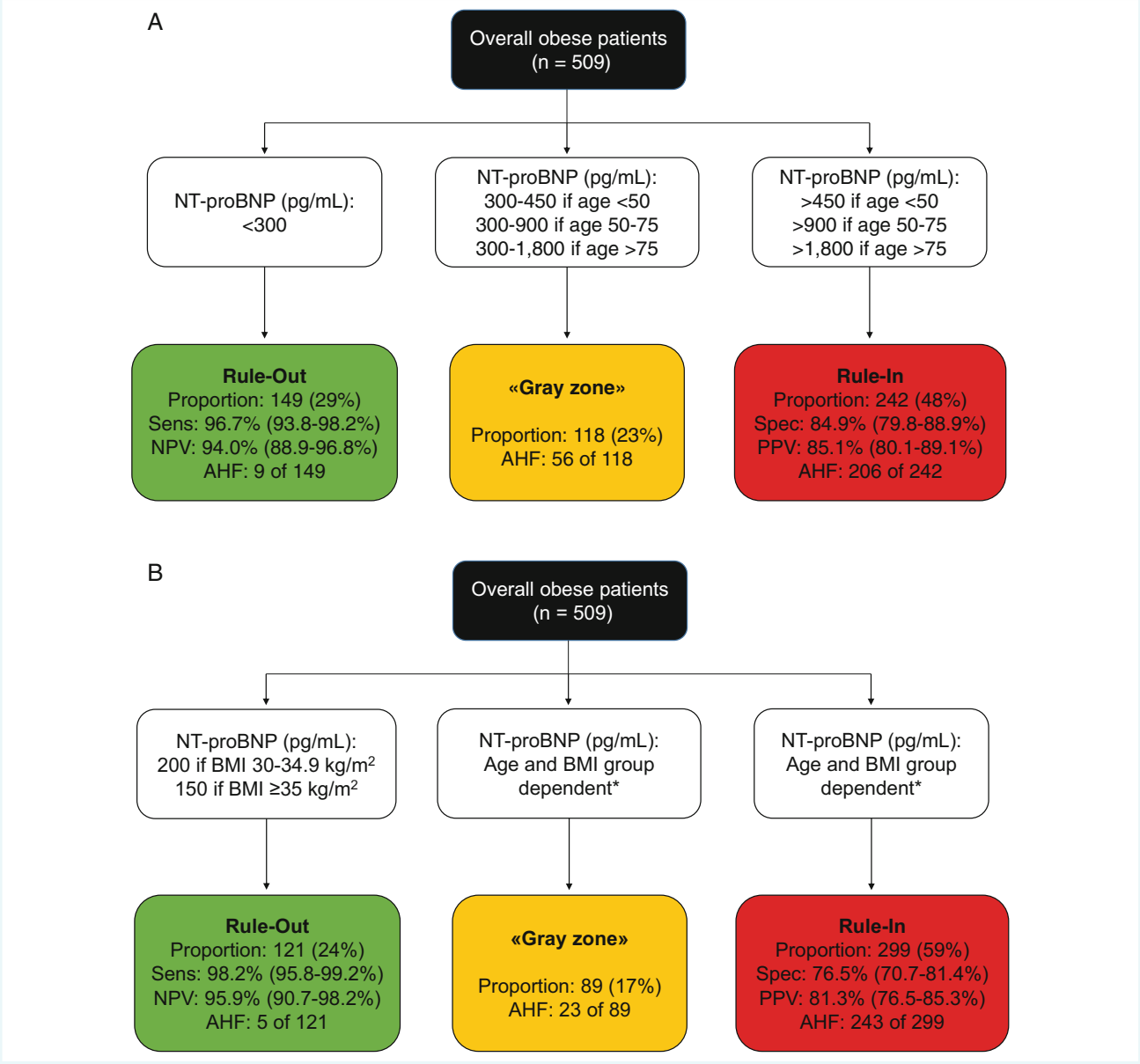


Figure 2 Obese patient stratification towards rule out, 'gray zone' and rule in when applying: (*A*) the currently recommended age-adjusted cut-off concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for the diagnosis of acute heart failure (AHF); or (*B*) the cut-off concentrations reduced by one third in patients with a body mass index (BMI) 30–34.9 kg/m^2 and by half in those with a BMI ≥35 kg/m^2. *If the BMI is 30–34.9 kg/m^2, the NT-proBNP rule-in cut-off is 300 ng/L for patients <50 years old, 600 ng/L for patients 50–75 years old, and 1200 ng/L for patients >75 years old. If the BMI is ≥35 kg/m^2, the NT- proBNP rule-in cut-off is 225 ng/L for patients <50 years old, 450 ng/L for patients 50–75 years old, and 900 ng/L for patients >75 years old. NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

overlap in haemodynamic stress and metabolic interactions affecting NT-proBNP levels in obese patients.[6] One further finding which might partly but not fully explain the lower diagnostic accuracy of NT-proBNP is the higher proportion of HF with preserved ejection fraction (HFpEF) patients among the obese with AHF. Notably, although the higher prevalence of HFpEF may partly explain NT-proBNP lower accuracy among the obese, further factors need to be accounted for to explain the overall lower NT-proBNP concentrations in obesity. In the study at hand, HFpEF patients with obesity had significantly lower NT-proBNP values as compared to the non-obese HFpEF patients. Fourth, in this study, currently recommended NT-proBNP cut-offs performed well in non-obese patients and were comparable to other cohorts with widely overlapping 95%CIs.[5,24–27] Although sensitivity, NPV, specificity, and PPV across the pre-defined BMI groups were high, in obese patients sensitivity and NPV for rule out were significantly lower than in

Table 4 Performance of N-terminal pro-B-type natriuretic peptide cut-off concentrations for the diagnosis or exclusion of acute heart failure

	Used cut-off concentration	Sensitivity, % (95% CI)	NPV, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)
Diagnostic performance of age-independent exclusionary ('rule-out') cut-off concentration					
Non-obese patients ($n = 1529$)	Currently recommended cut-off (300 ng/L)	98.7 (97.6–99.3)	97.7 (95.8–98.8)	55.9 (52.3–59.4)	69.0 (66.2–71.7)
Obese patients ($n = 509$)	Currently recommended cut-off	96.7 (93.8–98.2)	94.0 (88.9–96.8)	58.8 (52.5–64.9)	72.8 (68–77.1)
	Strategy A: Cut-off reduced by one third if BMI 30–34.9 kg/m^2, half if BMI ≥35 kg/m^2	98.2 (95.8–99.2)	95.9 (90.7–98.2)	48.7 (42.5–55.1)	68.6 (63.8–73)
	Strategy B: Cut-off reduced by one third	97.8 (95.3–99.0)	95.3 (90.2–97.8)	51.3 (44.9–57.5)	69.6 (64.8–74)
	Strategy C: Cut-off reduced by half	98.9 (96.8–99.6)	97.3 (92.3–99.1)	45 (38.8–51.3)	67.2 (62.4–71.6)
Diagnostic performance of confirmatory ('rule-in') age-dependent cut-off concentrations across all age groups					
Non-obese patients ($n = 1529$)	Currently recommended cut-offs: 450 ng/ml if age <50 years 900 ng/ml if age 50–75 years 1800 ng/ml if age >75 years	86.4 (83.8–88.6)	86.1 (83.4–88.4)	84.1 (81.3–86.5)	84.4 (81.7–86.8)
Obese patients ($n = 509$)	Currently recommended cut-offs:	76.0 (70.6–80.7)	75.7 (70.2–80.4)	84.9 (79.8–88.9)	85.1 (80.1–89.1)
	Strategy A: Cut-off reduced by one third if BMI 30–34.9 kg/m^2, half if BMI ≥35 kg/m^2	89.7 (85.5–92.8)	86.7 (81.4–90.6)	76.5 (70.7–81.4)	81.3 (76.5–85.3)
	Strategy B: Cut-off reduced by one third	84.9 (80.1–88.6)	82.2 (76.7–86.6)	79.4 (73.8–84.1)	82.4 (77.5–86.5)
	Strategy C: Cut-off reduced by half	90.8 (86.7–93.7)	87.2 (81.8–91.2)	71.8 (65.8–77.2)	78.6 (73.7–82.8)

BMI, body mass index; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

non-obese patients, resulting in a few AHF patients incorrectly triaged towards AHF rule out, and therefore missed. Fifth, the percentage of obese AHF patients not triaged towards AHF rule out or rule in by currently recommended NT-proBNP cut-offs and remaining in the NT-proBNP 'gray zone' was substantially higher when compared to non-obese patients (48% vs. 30%; $p < 0.001$). Sixth, reducing currently recommended cut-offs for AHF rule in and rule out by 33% in patients with BMI of 30.0–34.9 kg/m^2 and by 50% in patients with BMI ≥35.0 kg/m^2, roughly halved the number of obese patients with AHF remaining in the 'gray zone'. Thereby, the proportion of obese and non-obese AHF patients remaining in the 'gray zone' was comparable. Notably, the reduced cut-offs for obese patients significantly improved the sensitivity and NPV to rule out, at the cost of lower PPV and specificity to rule in AHF. With a relative weight of 1:2 for false positive versus true positive decisions, the net benefit favoured BMI-adjusted cut-offs. Seventh, in comparison with reducing the cut-offs for all obese patients by 33% or by 50%, the combined strategy of further stratifying obese patients according to their BMI achieved higher net benefit.

These findings have important clinical implications as they extend and corroborate the results of a study enrolling 1461 subjects (ICON-RELOADED).[25] ICON-RELOADED recruited younger patients (56.4 ± 15.7 years) with rather infrequent comorbidities, lower prevalence of AHF (19%), and higher BMI (32.0 ± 9.2 kg/m^2). ICON-RELOADED also documented lower sensitivity for NT-proBNP using the currently recommended rule-out cut-off in obese versus non-obese patients (72% vs. 90%). The consistency of the sensitivity deficit of the currently recommended NT-proBNP rule-out cut-offs and the high proportion of patients with AHF remaining in the 'gray zone' with currently recommended rule-in cut-offs justifies the clinical use of BMI-adjusted lower NT-proBNP cut-offs in patients with obesity.

These findings also highlight that NT-proBNP concentrations were disadvantaged in the methodology used to derive a clinical score for the prediction of HFpEF in a selected cohort of patients undergoing right heart catheterization.[28] Unfortunately, neither NT-proBNP nor BMI were used as quantitative variables,[28] which besides the undisputed lower accuracy of NT-proBNP for this entity contributed to their loss of independent diagnostic value in the final model.[28]

By adjusting NT-proBNP cut-off concentrations for obesity, a significant reduction in the proportion of patients consigned to the NT-proBNP 'gray zone' is achieved. The patients remaining in the 'gray zone' with values above the rule-out but below age-dependent rule-in cut-off concentration require further clinical investigations and likely more time and resources in the ED. Furthermore, initiation of timely therapy for AHF may be delayed which would reflect in worsening of prognosis. Thereby, although reducing the overall number of patients and the proportion of the ones with AHF remaining in the 'gray zone' may seem to be the dominant approach

from a cost-effectiveness perspective, future research is needed to precisely assess these outcomes. Specifically, the key application of NT-proBNP in the setting of acute dyspnoea rests on rule out of AHF. Accordingly, patients with results above this threshold will often need further assessment regardless of whether the peptide value exceeds the age-dependent rule-in concentration.

Notably, in patients with obesity, lower NT-proBNP cut-offs can only partly compensate for NT-proBNP slightly lower diagnostic accuracy. When comparing obese to non-obese patients, not only left ventricular pressures but also other factors have been described to impact NT-proBNP concentrations. These factors include but are not limited to: larger distribution volume, epicardial fat, glycosylation leading to loss of proBNP processing and/or a lower immunoreactive signal thus 'hiding' NT-proBNP from many immunoassays, the accelerated clearance of infused BNP observed in the obese.[6,10,29–31] Fortunately, with an AUC as high as 0.89 (vs. 0.94 in non-obese patients), even in obese patients presenting to the ED with acute dyspnoea, NT-proBNP remains the single clinical variable with by far the highest diagnostic accuracy.

BASEL V has important methodological strengths including its large sample size, highly representative patient population for acute dyspnoea and AHF,[13] and adjudicated final diagnosis by two independent cardiologists/internists according to current guidelines. To maximize the diagnostic adjudication accuracy, natriuretic peptide incorporation is necessary. To minimize the inclusion bias risk, different natriuretic peptide (BNP) was used for diagnostic adjudication in most patients.[1,24] Including BNP/NT-proBNP in the final adjudication was necessary to maximize the accuracy of the final diagnosis adjudication. Notably, in obese patients, no formal adjustment of the recommended cut-offs was used in the interpretation of BNP for the final adjudication of the diagnosis leading to ED presentation with shortness of breath. BNP and NT-proBNP were rather used as a quantitative marker of haemodynamic stress complementing all the available clinical information.

This study also has several limitations. First, its findings are specific to patients with acute dyspnoea in the ED and do not apply to NT-proBNP for screening in asymptomatic patients or patients presenting to an outpatient clinic.[1] Second, despite the strong methodology with central diagnostic adjudication, a few patients may still have been misclassified as either AHF or non-AHF. However, it is unlikely that this inherent limitation might have influenced the main findings. Third, this study required written informed consent. Therefore, small selection bias towards the enrolment of patients eligible to provide it was unavoidable. Fourth, due to hypervolaemia explaining excess body weight, some AHF patients are reclassified to a higher BMI group. This might have rather underestimated the improvement in diagnostics achieved by obesity adapted cut-offs for NT-proBNP. Notably, with currently available tools, this cannot be reasonably adjusted for and reflects the clinical reality in the ED setting. Future imaging studies quantifying euvolaemic body mass may be able to account for this bias. Fifth, as patients on chronic haemodialysis were excluded, we cannot comment on cut-offs in this patient population. Sixth, the non-obese patients' group also included patients with anorexia. Underweight may also have an impact on NT-proBNP concentrations and needs further investigation. Seventh, including BNP and NT-proBNP concentrations in the final adjudication allowed to maximize the accuracy of the final diagnosis adjudication, but may have introduced inclusion bias for the assessment of their diagnostic accuracy.

Conclusions

Reducing currently recommended NT-proBNP cut-offs for rule in and rule out of AHF by 33% in patients with BMI of 30.0–34.9 kg/m^2 and by 50% for BMI ≥35.0 kg/m^2 seems to further increase its clinical utility in the early diagnosis of AHF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Appendix

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