Age-adjusted natriuretic peptide thresholds for a new diagnosis of heart failure in the community: diagnostic accuracy study

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Abstract

Background

European Society of Cardiology (ESC) chronic heart failure (HF) guidelines recommend a single N-terminal pro-B-type natriuretic peptide (NT-proBNP) threshold of ≥125pg/mL for specialist referral in symptomatic patients, however, natriuretic peptide levels increase with age.

Objectives

We aimed to assess NT-proBNP test performance at age-adjusted thresholds recently proposed by the ESC Heart Failure Association (HFA).

Methods

Diagnostic accuracy study using linked primary and secondary care data (2004-2018) in England. NT-proBNP test performance at ESC HFA age-adjusted rule-in thresholds (≥125pg/mL, ≥250pg/mL, ≥500pg/mL for <50years, 50–74years, and ≥75years, respectively) and a high-risk threshold (≥2,000pg/mL) was assessed overall, by sex and body mass index (BMI) with ESC's suggested threshold reductions for obesity.

Results

Of 155,347 patients with NT-proBNP tests performed, 14,585 (9.4%) were diagnosed with HF. Current ESC single threshold of ≥125pg/mL had sensitivity 94.6% (95% confidence interval [CI] 94.2-95.0) and specificity 50.0% (49.7-50.3). Age-adjusted thresholds had reduced sensitivity (83.5%, 88.5%, 84.4%) but increased specificity (77.6%, 67.8%, 63.5%) across the respective age groups. The high-risk threshold had sensitivity 38.9% (38.1-39.7) and specificity 96.1% (96.0-96.2). A high BMI was associated with lower sensitivity at each age-adjusted threshold which improved with adjustment by obesity category. Test performance was similar in women and men.

Conclusion

At ESC HFA age-adjusted thresholds, the number of referrals required for HF diagnostic assessment are substantially reduced, but with some (likely lower risk) cases initially being undetected. Lower thresholds for patients with obesity are needed to avoid missing HF cases, but there is no need for adjustment by sex.

Key words: Heart failure, diagnosis, natriuretic peptide testing, diagnostic accuracy

Introduction

Early diagnosis of heart failure (HF) allows timely initiation of treatments which can prevent hospitalisation, improve quality of life and extend survival.[1] However, the key symptoms of HF – breathlessness, exhaustion and ankle swelling – are common and have a variety of causes.[2,3] Natriuretic peptides (NP) are an important part of the HF diagnostic pathway,[4] and international guidelines recommend carrying out an NP test with referral for echocardiography and specialist assessment if the level is raised.[5-7] A negative test can be useful to rule out HF, and consider other causes, but this depends upon the threshold set.[4] NP level at the time of diagnosis is also predictive of outcome including HF-related hospitalisation and survival.[8]

Echocardiography is a limited resource in most health systems globally therefore NP testing is important to prioritise those patients most likely to have HF for imaging and referral for specialist review.[9] This also reduces the possibility of overdiagnosis. B-type NP and N-terminal pro-B-type NP tests are used in clinical practice, although NT-proBNP is becoming the predominant test as it is more stable and also unaffected by neprilysin inhibition.[10] The American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA)[6] and European Society of Cardiology (ESC)[7] HF guidelines currently recommend a single NT-proBNP cut-off below 125pg/mL to rule out chronic HF in the community,[7] however, patient factors including age, sex and body mass index (BMI), as well as co-morbidities and therapies, can influence the level found on testing.[11]

NT-proBNP levels increase with age which can be challenging for interpretation of test results in both older and younger patients.[12] Older patients will be more likely to have a positive NT-proBNP test requiring further investigation, and younger patients may be missed if the level is below the threshold value required for referral. Higher NT-proBNP levels are also found in women compared to men.[13] A high BMI is associated with lower NT-proBNP

levels, which could lead to patients with obesity being initially falsely reassured they do not have HF leading to diagnostic delay. Current guidelines have the same testing thresholds across age strata, sex, and BMI.

In 2023, the ESC Heart Failure Association (HFA) published a practical algorithm for early diagnosis of HF proposing age-adjusted rule-in NT-proBNP thresholds: ≥125pg/mL for patients aged under 50 years, ≥250pg/mL for patients aged 50-74 years, and ≥500pg/mL for patients 75 years and over.[14] The ESC HFA also suggested adjustment for obesity class I, II and III by lowering the NT-proBNP threshold by 25%, 30% and 40% in patients with BMI 30-34.9kg/m^2, 35-39.9kg/m^2 and ≥40kg/m^2, respectively.

Our aim was to assess NT-proBNP test performance for HF diagnosis at the ESC HFA age-adjusted thresholds overall, in women and men separately, and BMI with additional adjustment by obesity category.

Methods

We analysed the Diagnose-NP diagnostic accuracy study dataset. The methods for the Diagnose-NP study have been described elsewhere.[15] In brief, it is a population-based cohort using primary care data from the Clinical Practice Research Datalink (CPRD) Gold and Aurum databases linked to inpatient Hospital Episode Statistics (HES) admitted patient care data and Index of Multiple Deprivation (IMD) socioeconomic data in England. The combined CPRD databases contain data from over 1,400 general practices in the UK, which is around 15% of general practices overall, and have been shown to be representative of the general population.[16]

Patients aged 45 years and over in the two CPRD databases with an NT-proBNP test in their primary care record between 1st January 2004 and 31st December 2018 were included. Patients entered the cohort on the date of their NT-proBNP test and exited the cohort on the

date of their HF diagnosis or six months after their NT-proBNP test date if they were not diagnosed with HF. Patients with a previous diagnosis of HF were excluded. Patients were only included if their primary care records were deemed acceptable for research purposes (a CPRD quality measure), eligible for linkage, and had been registered at a practice for at least 12 months. NT-proBNP tests and HF diagnosis codes were identified in CPRD using clinical coding lists (see Supplementary Material) derived from the NHS terminology and classifications browser and the Quality and Outcomes Framework guidance.[17]

NT-proBNP testing (index test)

NT-proBNP level was analysed both as a continuous and categorical variable using ACC/AHA/HFSA and ESC chronic HF guideline (NT-proBNP ≥125pg/ml)[7] and ESC HFA age-adjusted[14] (see Figure 1) referral thresholds for chronic HF diagnosis. NT-proBNP test performance at the ESC HFA high-risk threshold (NT-proBNP >2,000pg/mL) for rapid referral (to have echocardiography and specialist review within two weeks) was also explored. Subgroup analyses were carried out for women and men, and by obesity category (including adjustment of the threshold for obesity categories I, II and III).

Heart failure diagnosis (reference standard)

The primary outcome of HF diagnosis within six months of the most recent NT-proBNP test was obtained from either a diagnostic code entered in the CPRD database or from HES admitted patient care data based on hospital admission for HF or echocardiography findings consistent with HF. HF diagnoses from primary care were also validated through data linkage with HES using International Classification of Diseases, 10th revision codes (see Supplementary Material).

Statistical analysis

Sociodemographic variables were summarised with mean and standard deviation (SD) for continuous variables except NT-proBNP, and frequencies and percentages for categorical variables. These were estimated for participants with a NT-proBNP test overall, for participants split by age group (under 50 years, 50-74 years and ≥75 years), for women and men separately, and by BMI category (underweight <18.5kg/m^2, healthy weight 18.5-24.9kg/m^2, overweight 25-29.9 kg/m^2, obesity class I 30.0-34.9kg/m^2, class II 35.0-39.9kg/m^2, and class III ≥40kg/m^2).

Diagnostic test accuracy for HF diagnosis was assessed by calculating sensitivity, specificity, positive predictive values (PPV), negative predictive value (NPV), likelihood ratio, and diagnostic odds ratio using the 'epitools' package.[18] Exact confidence intervals (CIs) for proportions were calculated using the binomial distribution. CIs for ratios were calculated using the Wald's normal approximation. Receiver operating characteristic (ROC) curves were plotted to assess overall test performance. The area under the ROC curve (AUC) was estimated using the 'pROC' package.[19] All analyses were done in R (version 4.4.0) and used a 0.05 threshold to define statistical significance.

The protocol for the Diagnose-NP study was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (MHRA) (ISAC protocol number 19_136). Ethics approval for observational research using CPRD with approval from ISAC was granted by a National research Ethics Service committee (Trent MultiResearch Ethics Committee, reference number: 05/MRE04/87).

Results

In total, 155,347 patients had an NT-proBNP test recorded in their primary care record with a mean (SD) age of 61.1 years (11.0), more females (57.6%, n=89,464) and the majority of white ethnicity (91.2%, n=141,661). All five deprivation quintiles were equally represented

(Table 1). Of those with BMI recorded (96.3%), the mean BMI was 29.5kg/m^2 (6.4). Smoking was common with two thirds (67.2%) being current or former smokers. Long-term conditions associated with developing HF were also prevalent in those undergoing testing, with hypertension (59.0%, n=91,622) and diabetes (25.7%, n=39,886) being particularly high. Compared to younger age-groups, participants over 75 years were more likely to be female (64.9%, n=10,841) and had more long-term conditions except diabetes (21.0%, n=3,505). The proportion of those classed in the lowest deprivation quintile was highest in the under 50 years and lowest in those over 75 years (under 50 years 26.5%, n=8,722; 50-74 years 17.6%, n=18,584; ≥75 years 13.3%, n=2,221). Smoking was more common in men compared to women (76.9% vs 60.1% respectively being current or former smokers) (Table1). The deprivation quintiles and prevalence of long-term conditions were similar across men and women. Compared to other BMI categories, those underweight were more likely to be female (75.1%, n=1,859) and those with obesity class III (BMI 30-34.9 kg/m^2) were more likely to be in the lowest deprivation quintile (28.2%, n=2,773) and to have diabetes (43.2%, n=4,257) (Table 2).

Heart failure diagnosis

A total of 14,585 (9.4%) were diagnosed with HF within six months of NT-proBNP testing overall, including a higher proportion of those over 75 years compared to the younger age groups (3.8%, 9.8% and 17.5% in those under 50 years, 50-74 years and ≥75 years, respectively) and more men (11.2%) than women (8.2%). The proportion of people diagnosed with HF decreased across increasing BMI categories, with the highest proportion in those underweight (14.3%, 11.3% 9.3% and around 8% in those underweight, healthy weight, overweight and obesity, respectively).

The time between NT-proBNP test and subsequent HF diagnosis was a median of 26 days (IQR 7-64) however nearly 4 in 10 people waited six weeks or more (37.9%, n=5,527) to

receive a diagnosis (Table 1). Overall, 5,359 patients (36.7%) had a HF diagnosis within two weeks, and this only increased slightly to 45% (n=2,549) for those with a NT-proBNP test above 2,000pg/mL. For those above this threshold, participants under 50 years had the shortest delays, with median time between test and diagnosis of 12 days (IQR 3-34), 53% (n=207) had a diagnosis within two weeks and 20% (n=79) waited over six weeks. For other subgroups (based on age, sex and BMI), the median time to diagnosis was about 15 to 20 days. In the high-risk category of NT-proBNP above 2,000pg/ml, around 45% had a diagnosis within two weeks and around 30% waited over six weeks.

NT-proBNP testing

Of 155,347 with NT-proBNP tests, 32,882 (21.2%) were under 50 years, 105,771 (68.1%) were 50-74 years and 16,694 (10.7%) were aged 75 years or over. 65,883 (42.4%) were men and 89,464 (57.6%) were women. The median NT-proBNP level was 143pg/mL (IQR 60-413) overall, 59pg/mL (30-123) in people under 50 years, 163pg/mL (74-448) in those aged 50-74 years, 413pg/mL (174-1251) in those ≥75 years, 148pg/mL (68-377) in women and 134pg/ml (51-484) in men. (Table 1). Median NT-proBNP was 305pg/mL (132-906) in those underweight, 204pg/mL (85-634) in those with healthy weight, 145pg/mL (61-421) in those overweight, 119pg/mL (51-134) with obesity class I, 104pg/mL (49-265) with class II and 101pg/mL (47-245) for those in class III. (Table 2)

The corresponding median NT-proBNP levels in patients with a HF diagnosis were 1,358pg/mL (534-3,230) overall, 831pg/mL (206-2,541) in those aged <50 years, 1,301pg/mL (529-3,057) in those aged 50-74 years, 1,866pg/mL (741-4,089) in participants aged 75 years and over, 1,506pg/mL (584-3,471) in men, 1,224pg/mL (495-2,989) in women, 1,807pg/mL (738-4,699) in those underweight, 1,881pg/mL (703-4,310) with those at healthy weight, 1,412pg/mL (560-3,390) in those overweight, 1,132pg/mL (456-2,528) for those with obesity class I, 868pg/mL (371-1,905) with class II and 792pg/mL (274-1,906) for those in class III.

NT-proBNP diagnostic test accuracy

For all those with an NT-proBNP test, the current single NT-proBNP threshold ≥125pg/mL had sensitivity 94.6% (95% confidence intervals [CI] 94.2-95.0) and specificity 50.0% (49.7-50.3), and for high risk (≥ 2,000pg/mL) sensitivity 38.9% (38.1-39.7) and specificity 96.1% (96.0-96.2) (Table 3).

The ESC HFA age-adjusted thresholds for <50 years, 50-74 years and ≥75 years had sensitivities of 83.5% (81.3 -85.5), 88.5% (87.9-89.1) and 84.4% (83.0-85.7), respectively. The specificity was highest in the <50 years group at 77.6% (77.2-78.1), then 67.8% (67.5-68.0) in 50-74 years, and 63.5% (62.7-64.3) in ≥75 years, respectively (Table 4). The overall performance in using NT-proBNP was statistically significantly better for people under 50 years (AUC 0.89, 95% CI=0.88 to 0.90) compared to other age groups (0.867, 95% CI 0.863 to 0.87 for age 50-74 years, 0.81, 95% CI 0.80 to 0.82 for age ≥75 years) (Figure 2).

For NT-proBNP testing, PPV improved across age groups from 13.0% (12.2-13.7), to 23.1% (22.6-23.5), and 32.8% (31.7-33.9) in <50 years, 50-74 years and ≥75 years groups, respectively due to the increasing prevalence of HF with age. NPV was 95% or above across all categories (Table 3).

Sensitivities at all three age groups were similar in women and men (Tables 4 and 5 respectively). However, specificity was improved to above 80% for men below the age of 50 years. The overall performance NT-proBNP testing was similar for men and women (Figure 3) and across the obesity classes (Figure 4).

For all age-adjusted thresholds, sensitivity decreased with increasing obesity category (Tables 6-8). By lowering the NT-proBNP age-adjusted thresholds by 25%, 30% and 40% in obesity category I, II and III, respectively, the sensitivity and specificity was comparable to the test performance seen in the cohort overall. The same comparable performance applied to those

overweight and at healthy weight at the age-adjusted thresholds (Tables 9 and 10) but this did not apply to those who were underweight, for which specificity was below 30% at the ACC/ AHA/HFSA and ESC 125pg/mL threshold and all specificities were consistently lower than those for the cohort overall (Table 11).

Discussion

Summary of findings

In this real-world diagnostic accuracy study, ESC HFA age-adjusted NT-proBNP thresholds were associated with lower sensitivity but higher specificity compared to the single ACC/AHA/HFSA and ESC recommended threshold of 125pg/mL. The performance at these thresholds was similar in women and men. Obesity categories were associated with lower sensitivity, which improved using the adjustment factors suggested by ESC HFA. A very elevated NT-proBNP >2,000pg/mL was highly suggestive of HF.

Strengths and limitations

This study used real world evidence to evaluate NT-proBNP test accuracy in 155,347 primary care patients who underwent testing. This is a much larger sample size than any prospective HF diagnostic accuracy study in primary care to date.[20] The large dataset allowed further exploration of age-adjusted thresholds overall, in both sexes, and by obesity category which would not be possible in smaller studies.

There are limitations of routinely collected data including accuracy of clinical coding. The reference standard was the presence or absence of a diagnostic code of HF, and the codes entered into primary care records are for clinical use rather than research purposes. However, HF as a condition is generally well recorded over the time the study was conducted.[21] The type of HF - heart failure with reduced ejection fraction (HFrEF) or heart failure with

preserved ejection fraction (HFpEF) - was also not possible to establish given the limited use of HFrEF and HFpEF codes in primary and secondary care records during the study period.[22]

The study was performed in England where the National Institute for Health and Care Excellence (NICE) recommend a NT-proBNP threshold of 400pg/mL for referral for outpatient diagnostic assessment.[5] Patients with HF and a test result below the NICE threshold may therefore not have initially been referred via this diagnostic pathway so could potentially appear as false negative cases. However, these patients are likely to have presented to the healthcare system via other routes such as emergency admission which is why a limit of six months was set to allow time for a HF diagnostic code to be entered in the primary care record.

The NP level can be influenced by factors we did not explore such as other long-term conditions and medications.[23] However, ACC/AHA/HFSA and ESC guidelines do not currently recommend stratifying by these factors, so our findings reflect current practice. Moreover, patients with long-term conditions which raise their NP level, particularly atrial fibrillation (AF) and chronic kidney disease (CKD), are likely to be captured in the higher age-adjusted thresholds, so we focused on the impact of BMI in this analysis.

Comparison with existing literature

Epidemiological and mechanistic studies have previously shown that NP levels increase with age.[24-27] In 911 healthy adults from the Framingham Heart Study in the United States of America, the strongest predictors of higher NP levels were older age and female sex.[24] A population-based cohort study of 2,459 older adults in Germany also reported an age-related incremental increase in NT-proBNP levels. In apparently healthy individuals aged 65 years and over, 27% of men and 45% of women had a NT-proBNP level above the 125pg/mL threshold recommended by ACC/AHA/HFSA and ESC guidelines.[26] The need for age

adjusted thresholds to allow meaningful interpretation of NP results has therefore previously been proposed. A study of 5,508 primary care patients, published in 2010, suggested thresholds of 50pg/mL, 75pg/mL and 250pg/mL for age groups <50 years, 50-75 years and above 75 years, respectively to improve test performance.[12] However, these thresholds are yet to be adopted in international guidance. A recent paper describing the conceptual basis for a 'Universal Definition of Heart Failure' acknowledged the impact of age and sex on NP level and suggested potential diagnostic thresholds stratified by age and sex.[28] In increments of ten years from less than age 60 years to above age 80 years the threshold, starting at >75pg/mL for men age less than 60 years, increased by 50pg/mL for each decade and was 50pg/mL higher for women than men in the same age group. These are much lower than the ESC HFA age-adjusted thresholds tested in our study. The sensitivities at the lower thresholds are likely to be better, but many more echocardiography assessments would be needed, potentially overwhelming the service. Our data also suggest adjustment by sex is not necessary in contrast to previous studies.

The inverse relationship between BMI and NP levels leads to challenges in the interpretation of NT-proBNP test results in patients with obesity and suspected HF. Potential mechanisms for lower NP levels in the presence of obesity include higher glomerular filtration, peri-atrial fat reducing stretch and high expression of NT-proBNP receptors on adipocytes reducing circulating levels.[29] The relationship may be bidirectional whereby lack of circulating NP makes patients more prone to obesity, as well as obesity lowering NP levels. Once diagnosed, an obesity paradox has been observed where survival rates are better in people with overweight and obesity compared to normal weight[30], although NT-proBNP level remains an independent predictor of prognosis and the obesity paradox has more recently been questioned.[8,31] Our findings suggest the need for NT-proBNP age-adjusted thresholds to avoid missing more cases of HF in patients living with obesity.

Conversely, specificity of NT-proBNP was particularly low in the underweight group. There may be several clinical explanations for this. Patients with a low BMI may have an underlying condition, such as malignancy or frailty, which is associated with higher NT-proBNP levels, so their test result was above the threshold for referral, but they did not have a diagnosis of HF.[32]

Implications for policy and practice

In the UK, national guidance from NICE recommends that symptomatic patients are referred and have echocardiography and specialist assessment within six weeks if NT-proBNP is 400pg/mL or above, and within two weeks if NT-proBNP is over 2,000pg/mL.[5] However, healthcare systems **globally** have finite budgets and are increasingly under strain due to resource constraints. Patients are frequently hospitalised to receive a diagnosis of HF, and our **UK** data show most patients, including those at highest risk (NT-proBNP>2,000pg/mL), wait more than the recommended time frames for assessment.[8] NP testing needs to be an effective triage tool to ensure those patients at highest risk have rapid access to echocardiography and specialist assessment to allow treatment initiation in the community and prevent hospitalisation. The use of age-adjusted cut-points could ensure older patients are not unnecessarily investigated for HF, avoiding the possibility of overdiagnosis, and younger and higher risk patients are seen sooner. This would mean more cases of HF may initially be missed in primary care, but with fewer people meeting the criteria for referral easing the burden on echocardiography and specialist cardiology services. For example, in our cohort, over a 14-year period, using the age-adjusted thresholds in place of the ACC/AHA/HFSA and ESC 125pg/mL threshold would result in 1,073 missed HF cases (~77 per year) but saving 27,508 echocardiography and specialist assessment appointments (~2,000 per year). Therefore, overall, the age-adjusted thresholds would lead to an 18% reduction in unnecessary referrals, but with around 7.4% of all those with HF missed by the

new approach. The cases which are initially undetected are likely to be low risk given our work showing baseline NT-proBNP level is directly related to HF-related hospitalisation and mortality.[8] Therefore, while some in the 'Grey Zone' between 125pg/mL and the age-adjusted thresholds could be diagnosed later this would free up capacity to allow those with high NT-proBNP values (who are currently waiting too long) to undergo echocardiography and specialist assessment. The new algorithm could therefore mean those most likely to benefit can be seen and treated more quickly.

This trade-off between a missed diagnosis and capacity within the HF diagnostic pathway is challenging for primary care clinicians, heart failure specialists, and for patients and their families. Generalists need to be aware of all the factors which influence NP levels and take these into account when interpreting test results and making the decision to refer for echocardiography and specialist assessment. For patients with an NP result near to the referral threshold, clinical acumen and repeat NP testing may be useful for those where a HF diagnosis is suspected. **The findings of this study should inform future guidelines to ensure recommended NP testing thresholds are evidence-based and include adjustments for patient characteristics such as age and obesity. NT-proBNP is currently still the most studied and reliable blood marker for HF diagnosis, but clinicians need to consider the impact of patient factors when interpreting test results and deciding, with the patient, on the most appropriate next step in the clinical pathway.**

More research is needed to explore the practicalities of implementing age-adjusted thresholds in practice, and further guidance is needed for how clinicians should manage patients in the 'Grey Zone'. Further work is also needed to consider threshold recommendations in key subgroups, such as AF and CKD although these factors both increase NP levels, so are more likely to fall within the age-adjusted rule in thresholds presented here. The ESC HFA position paper on age-adjusted NT-proBNP thresholds suggested the cut-points should be reduced by

25%, 30% and 40% for class I, II and III obesity, respectively, although this recommendation was based on consensus.[14] Our findings support the use of these adjustment factors by obesity category to avoid missing HF cases.

Globally, healthcare budgets and diagnostic pathways vary widely, and equitable allocation of healthcare resources for people with HF remains a challenge. The optimal NT-proBNP threshold will ultimately depend on the priorities and capacity of the national healthcare system.

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Disclosure of interest

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Figure legends

Figure 1. European Society of Cardiology Heart Failure Association algorithm for NT-proBNP testing to diagnose heart failure in the outpatient setting

Figure 2. ROC curve for HF diagnosis for NT-proBNP tests at ESC age-specific referral thresholds of participants aged under 50 years, 50-74 years and ≥75 years. AUC = area under the ROC curve; ESC = European Society of Cardiology; HF = heart failure; ROC = receiver operating characteristic; NT-proBNP=N-terminal pro B-type natriuretic peptide.

Figure 3. ROC curve for HF diagnosis for NT-proBNP tests at ESC and NICE referral thresholds for men and women separately. AUC = area under the ROC curve; ESC = European Society of Cardiology; HF = heart failure; ROC = receiver operating characteristic; NICE = National Institute for Health and Care Excellence; NT-proBNP=N-terminal pro-B-type natriuretic peptide

Figure 4. ROC curve for HF diagnosis for NT-proBNP tests at ESC and NICE referral thresholds for obesity classes I, II and III. AUC = area under the ROC curve; ESC = European Society of Cardiology; HF = heart failure; ROC = receiver operating characteristic; NICE = National Institute for Health and Care Excellence; NT-proBNP=N-terminal pro B-type natriuretic peptide

Figures

Figure 1

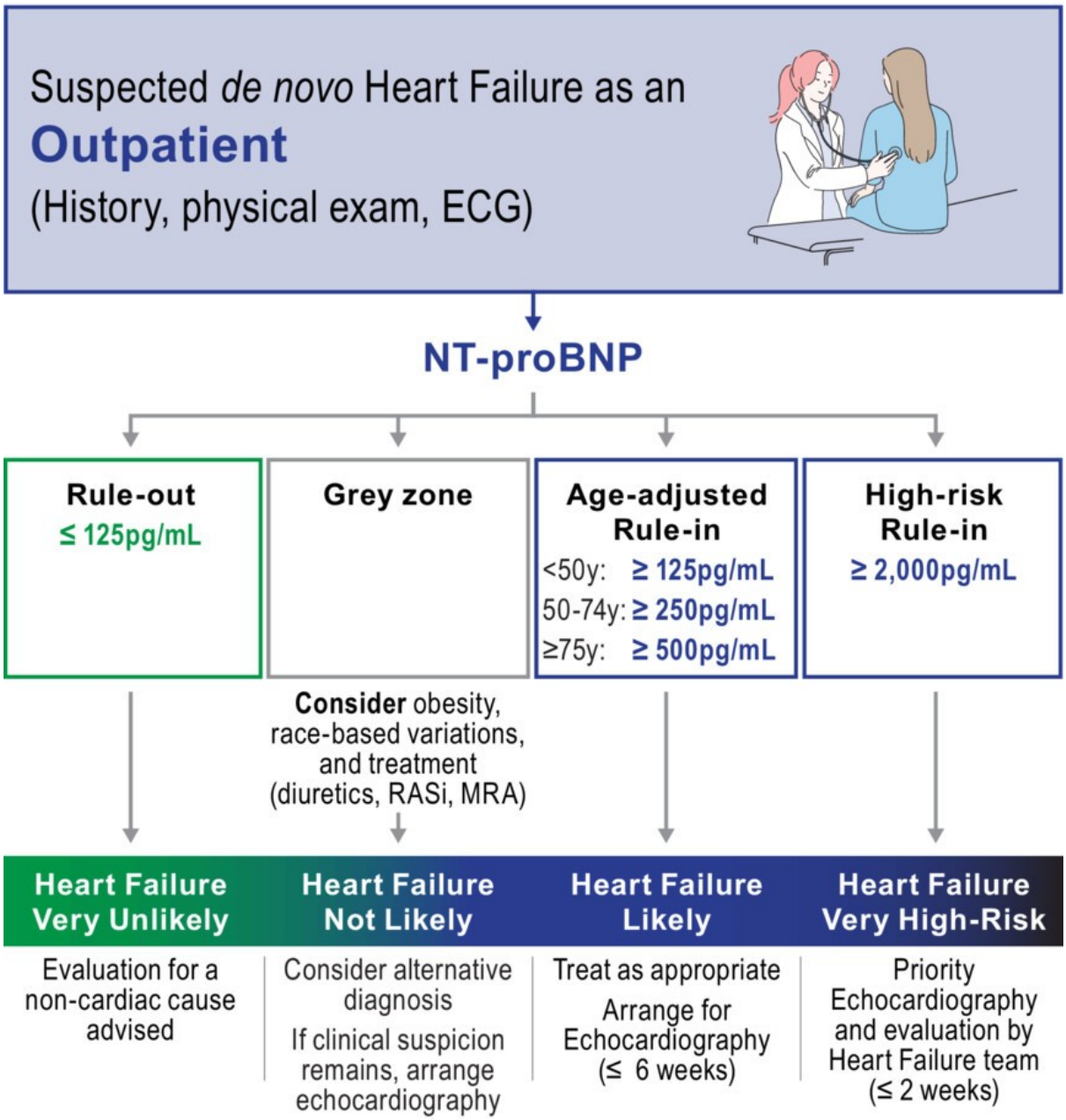

Figure 2

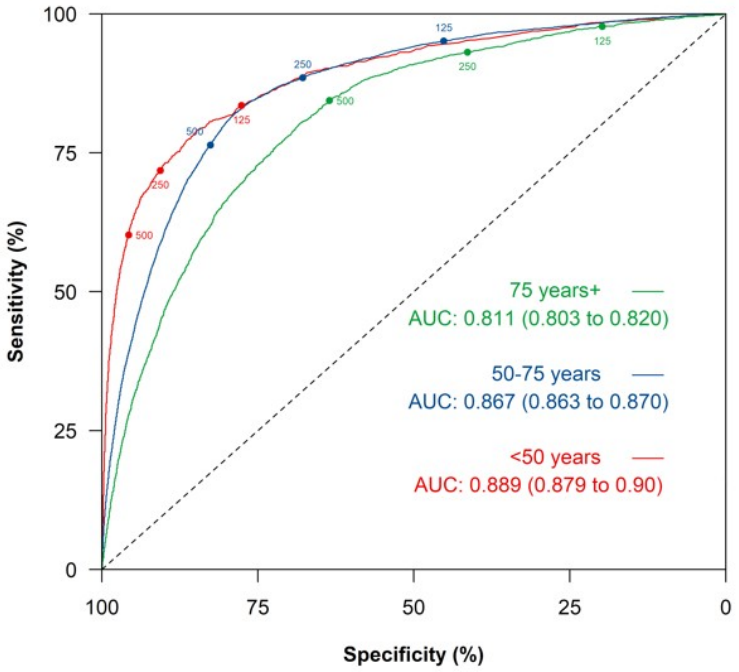

Figure 3

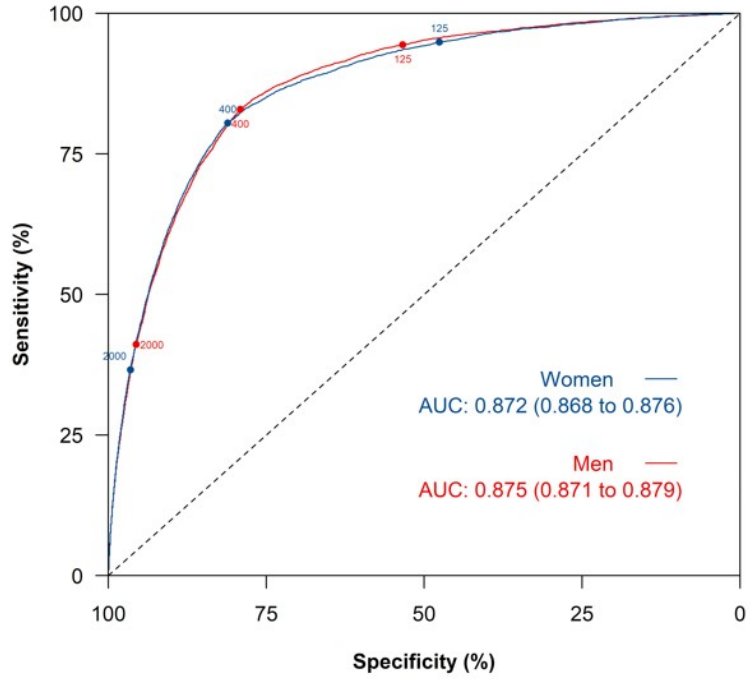

Figure 4

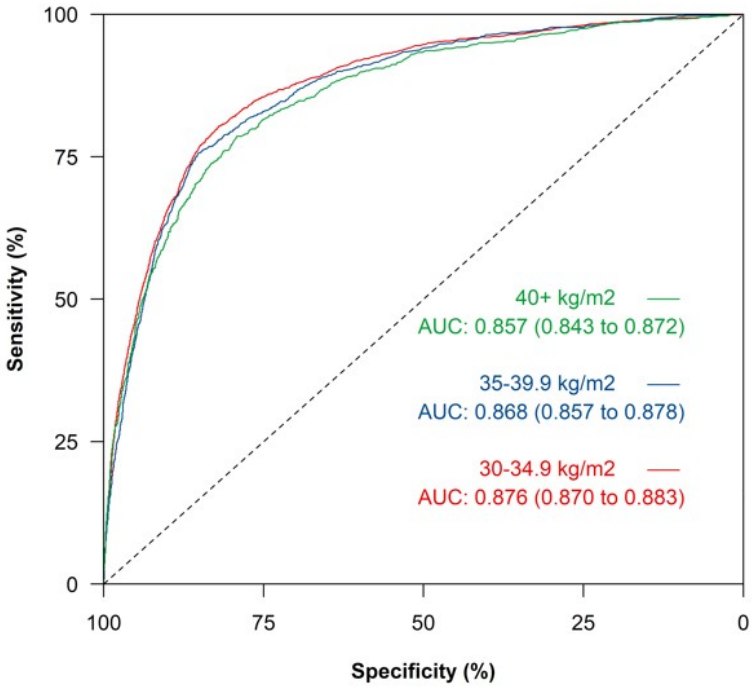
100
75
50
25
0
Sensitivity (%)
100
75
50
25
0
Specificity (%)
40+ kg/m2
AUC: 0.857 (0.843 to 0.872)
35-39.9 kg/m2
AUC: 0.868 (0.857 to 0.878)
30-34.9 kg/m2
AUC: 0.876 (0.870 to 0.883)

Table 1. Summary of characteristics for primary care patients undergoing NT-proBNP testing overall and by age and sex.

Characteristic	All	<50years	50-74years	≥75years	Men	Women
N	155347	32882	105771	16694	65883	89464
Age, years, mean (SD)	61.1 (11.0)	46.3 (1.7)	62.6 (6.7)	80.4 (4.4)	60.4 (10.77)	61.6 (11.3)
Sex, female n (%)	89464 (57.6)	18336 (55.8)	60287 (57.0)	10841 (64.9)	0 (0.0)	89464 (100.0)
Ethnicity, n (%)						
White	141661 (91.2)	28266 (86.0)	97722 (92.4)	15673 (93.9)	60290 (91.5)	81371 (91.0)
Non-white	10946 (7.05)	3651 (11.1)	6451 (6.1)	844 (5.06)	4337 (6.58)	6609 (7.39)
Missing	2740 (1.8)	965 (2.9)	1598 (1.5)	177 (1.1)	1256 (1.9)	1484 (1.7)
BMI (kg/m2), mean (SD)	29.51 (6.42)	31.69 (7.39)	29.27 (6.06)	26.61 (5.01)	29.31 (5.75)	29.66 (6.87)
Smoking status, n(%)						
Never	50629 (32.6)	10859 (33.0)	33002 (31.2)	6768 (40.5)	15137 (23.0)	35492 (39.7)
Former	79714 (51.3)	14240 (43.3)	57059 (53.9)	8415 (50.4)	39116 (59.4)	40598 (45.4)
Current	24691 (15.9)	7730 (23.5)	15547 (14.7)	1414 (8.5)	11497 (17.5)	13194 (14.7)
Missing	313 (0.2)	53 (0.2)	163 (0.2)	97 (0.6)	133 (0.2)	180 (0.2)
IMD, quintile, n(%)						
Q1 (least deprived)	30085 (19.4)	5202 (15.8)	21193 (20.0)	3690 (22.1)	13048 (19.8)	17037 (19.0)
Q2	32861 (21.2)	5748 (17.5)	23288 (22.0)	3825 (22.9)	14384 (21.8)	18477 (20.7)
Q3	31593 (20.3)	6098 (18.5)	21768 (20.6)	3727 (22.3)	13560 (20.6)	18033 (20.2)
Q4	31187 (20.1)	7086 (21.5)	20879 (19.7)	3222 (19.3)	12967 (19.7)	18220 (20.4)
Q5 (most deprived)	29527 (19.0)	8722 (26.5)	18584 (17.6)	2221 (13.3)	11884 (18.0)	17643 (19.7)
Missing	94 (0.1)	26 (0.1)	59 (0.1)	9 (0.1)	40 (0.1)	54 (0.1)
Medical history, n(%)						
Diabetes	39886 (25.7)	8077 (24.6)	28304 (26.8)	3505 (21.0)	18625 (28.3)	21261 (23.8)
Hypertension	91622 (59.0)	13569 (41.3)	66660 (63.0)	11393 (68.2)	38456 (58.4)	53166 (59.4)
Atrial Fibrillation	17403 (11.2)	1162 (3.5)	13210 (12.5)	3031 (18.2)	8960 (13.6)	8443 (9.4)
Angina	14442 (9.3)	1413 (4.3)	10941 (10.3)	2088 (12.5)	7663 (11.6)	6779 (7.6)
Ischaemic Heart Disease	18007 (11.6)	2004 (6.1)	13611 (12.9)	2392 (14.3)	10443 (15.9)	7564 (8.5)
Myocardial infarction	9729 (6.3)	1256 (3.8)	7160 (6.8)	1313 (7.9)	6329 (9.6)	3400 (3.8)

Stroke	12629 (8.1)	1269 (3.9)	9277 (8.8)	2083 (12.5)	6040 (9.2)	6589 (7.4)
Valvular disease	5689 (3.7)	506 (1.5)	4234 (4.0)	949 (5.7)	2410 (3.7)	3279 (3.7)
Other CV disease	21438 (13.8)	2639 (8.0)	15561 (14.7)	3238 (19.4)	9724 (14.8)	11714 (13.1)
SBP (mmHg), mean (SD)	136.30 (16.90)	133.93 (16.65)	136.88 (16.74)	137.24 (17.95)	135.93 (16.49)	136.57 (17.19)
DBP (mmHg), mean (SD)	76.99 (10.32)	80.50 (10.21)	76.36 (10.06)	74.15 (10.43)	77.00 (10.53)	76.99 (10.16)
Total cholesterol (mmol/L), mean (SD)	4.87 (1.15)	5.10 (1.13)	4.81 (1.15)	4.79 (1.15)	4.53 (1.09)	5.12 (1.13)
NT-pro BNP (pg/ml), median (IQR)	143 (60,413)	59 (30,123)	163 (74,448)	413 (174,1251)	134 (51,484)	148 (68,377)
Time between NP test and HF diagnosis (days)	26 (7,64)	24 (7,65)	27 (7,65)	22 (7,60)	27 (8,65)	24 (7,63)
< 2 weeks, n(%)	5359 (36.7)	483 (38.3)	3722 (35.8)	1154 (39.6)	2606 (35.2)	2753 (38.3)
2-6 weeks, n(%)	3699 (25.4)	322 (25.6)	2641 (25.4)	736 (25.3)	1922 (26.0)	1777 (24.7)
>= 6 weeks, n(%)	5527 (37.9)	455 (36.1)	4048 (38.9)	1024 (35.1)	2824 (38.8)	2653 (36.9)

Abbreviations: BMI = body mass index; BNP = B-type natriuretic peptide; CV=cardiovascular; DBP = diastolic blood pressure; HF = heart failure; IMD = Index of Multiple Deprivation; IQR = interquartile range (25th and 75th percentiles); SD= standard deviation; NP = natriuretic peptide; Q = quintile; SBP = systolic blood pressure.

Table 2. Summary of characteristics for primary care patients undergoing NT-proBNP testing by BMI categories

Characteristic	Underweight	Healthy	Overweight	Obesity I	Obesity II	Obesity III	missing
N	2475	33988	51630	35704	15966	9843	5741
Age, years, mean (SD)	64.94 (11.6)	64.1 (11.3)	62.0 (10.7)	59.6 (10.2)	57.2 (9.7)	54.2 (8.9)	65.4 (13.7)
Sex, female n (%)	1859 (75.1)	20672 (60.8)	26938 (52.2)	19997 (56.0)	9944 (62.3)	6719 (68.3)	3335 (58.1)
Ethnicity, n (%)							
White	2304 (93.1)	31274 (92.0)	47073 (91.2)	32454 (90.9)	14479 (90.7)	8955 (91.0)	5122 (89.2)
Non-white	131 (5.29)	2136 (6.28)	3711 (7.19)	2706 (7.58)	1242 (7.78)	709 (7.2)	311 (5.42)
Missing	40 (1.6)	578 (1.7)	846 (1.6)	544 (1.5)	245 (1.5)	179 (1.8)	308 (5.4)
BMI (kg/m2), mean (SD)	17.08 (1.22)	22.67 (1.68)	27.49 (1.40)	32.21 (1.42)	37.13 (1.42)	44.74 (4.62)	-
Smoking status, n(%)							
Never	717 (29.0)	11661 (34.3)	16772 (32.5)	11138 (31.2)	4830 (30.3)	2986 (30.3)	2525 (44.0)
Former	953 (38.5)	16186 (47.6)	27196 (52.7)	19356 (54.2)	8636 (54.1)	5245 (53.3)	2142 (37.3)
Current	803 (32.4)	6117 (18.0)	7603 (14.7)	5172 (14.5)	2484 (15.6)	1610 (16.4)	902 (15.7)
Missing	2 (0.1)	24 (0.1)	59 (0.1)	38 (0.1)	16 (0.1)	2 (0.0)	172 (3.0)
IMD, quintile, n(%)							
Q1 (least deprived)	487 (19.7)	7525 (22.1)	10893 (21.1)	6342 (17.8)	2430 (15.2)	1223 (12.4)	1185 (20.6)
Q2	445 (18.0)	7696 (22.6)	11551 (22.4)	7220 (20.2)	2966 (18.6)	1661 (16.9)	1322 (23.0)
Q3	464 (18.7)	6896 (20.3)	10432 (20.2)	7496 (21.0)	3185 (19.9)	1910 (19.4)	1210 (21.1)
Q4	486 (19.6)	6408 (18.9)	10001 (19.4)	7352 (20.6)	3457 (21.7)	2269 (23.1)	1214 (21.1)
Q5 (most deprived)	591 (23.9)	5441 (16.0)	8726 (16.9)	7272 (20.4)	3916 (24.5)	2773 (28.2)	808 (14.1)
Missing	2 (0.1)	22 (0.1)	27 (0.1)	22 (0.1)	12 (0.1)	7 (0.1)	2 (0.0)
Medical history, n(%)							
Diabetes	366 (14.8)	5940 (17.5)	11773 (22.8)	11166 (31.3)	5896 (36.9)	4257 (43.2)	488 (8.5)
Hypertension	1103 (44.6)	17570 (51.7)	30196 (58.5)	22913 (64.2)	10815 (67.7)	6781 (68.9)	2244 (39.1)
Atrial Fibrillation	260 (10.5)	4349 (12.8)	6059 (11.7)	3716 (10.4)	1523 (9.5)	861 (8.7)	635 (11.1)
Angina	167 (6.7)	3035 (8.9)	5255 (10.2)	3638 (10.2)	1369 (8.6)	727 (7.4)	251 (4.4)
Ischaemic Heart Disease	208 (8.4)	3876 (11.4)	6655 (12.9)	4437 (12.4)	1644 (10.3)	860 (8.7)	327 (5.7)
Myocardial infarction	124 (5.0)	2158 (6.3)	3668 (7.1)	2278 (6.4)	855 (5.4)	433 (4.4)	213 (3.7)

Stroke	227 (9.2)	3092 (9.1)	4514 (8.7)	2739 (7.7)	1084 (6.8)	549 (5.6)	424 (7.4)
Valvular disease	99 (4.0)	1581 (4.7)	2082 (4.0)	1142 (3.2)	406 (2.5)	199 (2.0)	180 (3.1)
Other CV disease	364 (14.7)	5220 (15.4)	7602 (14.7)	4718 (13.2)	1865 (11.7)	1043 (10.6)	626 (10.9)
SBP (mmHg), mean (SD)	131.50 (19.07)	134.75 (17.77)	136.21 (16.60)	137.06 (16.27)	137.45 (16.07)	138.08 (16.48)	137.26 (18.85)
DBP (mmHg), mean (SD)	73.52 (11.10)	75.20 (10.30)	76.59 (10.09)	77.78 (10.10)	78.77 (10.12)	79.85 (10.43)	78.11 (11.15)
Total cholesterol (mmol/L), mean (SD)	4.97 (1.13)	4.94 (1.15)	4.88 (1.16)	4.84 (1.15)	4.79 (1.14)	4.75 (1.10)	5.07 (1.14)
NT-pro BNP (pg/ml), median (IQR)	305 (132,906)	204 (85,634)	145 (61,421)	119 (51,314)	104 (49,265)	101 (47,245)	184 (71,635)
Time between NP test and HF diagnosis (days)	22 (6,57)	24 (7,60)	26 (8,65)	28 (8,70)	28 (8,67.2)	27 (7,65)	18 (6,55.5)
< 2 weeks, n(%)	151 (42.5)	1456 (37.9)	1745 (36.4)	1023 (35.0)	418 (33.6)	273 (35.9)	293 (43.4)
2-6 weeks, n(%)	78 (22.0)	993 (25.9)	1206 (25.2)	740 (25.3)	321 (25.8)	196 (25.8)	165 (24.4)
>= 6 weeks, n(%)	126 (35.5)	1390 (36.2)	1838 (38.4)	1159 (39.7)	505 (40.6)	292 (38.4)	217 (32.1)

Table 3. Diagnostic test accuracy parameters for algorithm for the diagnosis of de novo chronic heart failure using NT-proBNP level, overall and for age subgroups, at the current ESC threshold and at thresholds adjusting for age and high risk

Test	Rule-in >=125 pg/mL	Rule-in age <50 years >=125 pg/mL	Rule-in age 50-74 years >=250 pg/mL	Rule-in age ≥75 years >=500 pg/mL	Rule-in Age-adjusted	Rule-in High risk >=2000 pg/mL
N	155347	32882	105771	16694	155347	155347
Prevalence, % (95% CI)	9.4 (9.2, 9.5)	3.8 (3.6, 4)	9.8 (9.7, 10)	17.5 (16.9, 18)	9.4 (9.2, 9.5)	9.4 (9.2, 9.5)
TP, n	13801	1052	9218	2458	12728	5674
FN, n	784	208	1193	456	1857	8911
FP, n	703	7069	30753	5035	42857	5424
TN, n	70397	24553	64607	8745	97905	135338
Sensitivity, % (95% CI)	94.6 (94.2, 95)	83.5 (81.3, 85.5)	88.5 (87.9, 89.1)	84.4 (83, 85.7)	87.3 (86.7, 87.8)	38.9 (38.1, 39.7)
Specificity, % (95% CI)	50 (49.7, 50.3)	77.6 (77.2, 78.1)	67.8 (67.5, 68)	63.5 (62.7, 64.3)	69.6 (69.3, 69.8)	96.1 (96, 96.2)
PPV, % (95% CI)	16.4 (16.1, 16.6)	13 (12.2, 13.7)	23.1 (22.6, 23.5)	32.8 (31.7, 33.9)	22.9 (22.5, 23.2)	51.1 (50.2, 52.1)
NPV, % (95% CI)	98.9 (98.8, 99)	99.2 (99, 99.3)	98.2 (98.1, 98.3)	95 (94.6, 95.5)	98.1 (98.1, 98.2)	93.8 (93.7, 93.9)
LR+ (95% CI)	1.89 (1.88, 1.91)	3.73 (3.62, 3.86)	2.75 (2.71, 2.78)	2.31 (2.25, 2.37)	2.87 (2.84, 2.9)	10.1 (9.77, 10.44)
LR- (95% CI)	0.11 (0.1, 0.12)	0.21 (0.19, 0.24)	0.17 (0.16, 0.18)	0.25 (0.23, 0.27)	0.18 (0.18, 0.19)	0.64 (0.63, 0.64)
DOR (95% CI)	17.61 (16.38,18.94)	17.55 (15.13, 20.46)	16.23 (15.26, 17.26)	9.36 (8.43, 10.42)	15.66 (14.9, 16.46)	15.89 (15.22, 16.59)

Abbreviations: CI=confidence interval; TP = true positives; FN = false negatives; FP = false positives, TN = true negatives; NPV=negative predictive value; PPV=positive predictive value. LR=likelihood ratio; DOR=diagnostic odds ratio.

Table 4. Diagnostic test accuracy parameters for algorithm for the diagnosis of de novo chronic heart failure using NT-proBNP level overall and for age subgroups, at the current ESC threshold and at thresholds adjusting for age and high risk, for women only

Test	Rule-in >=125 pg/mL	Rule-in age <50 years >=125 pg/mL	Rule-in age 50-74 years >=250 pg/mL	Rule-in age ≥75 years >=500 pg/mL	Rule-in Age-adjusted	Rule-in High risk >=2000 pg/mL
N	89464	18336	60287	10841	89464	89464
Prevalence, % (95% CI)	8 (7.9, 8.2)	2.8 (2.6, 3)	8.2 (8, 8.4)	15.9 (15.2, 16.6)	8 (7.9, 8.2)	8 (7.9, 8.2)
TP, n	6815	425	4350	1419	6194	2632
FN, n	368	86	603	300	989	4551
FP, n	43139	4376	17610	3227	25213	2858
TN, n	39142	13449	37724	5895	57068	79423
Sensitivity, % (95% CI)	94.9 (94.3, 95.4)	83.2 (79.6, 86.3)	87.8 (86.9, 88.7)	82.5 (80.7, 84.3)	86.2 (85.4, 87)	36.6 (35.5, 37.8)
Specificity, % (95% CI)	47.6 (47.2, 47.9)	75.5 (74.8, 76.1)	68.2 (67.8, 68.6)	64.6 (63.6, 65.6)	69.4 (69, 69.7)	96.5 (96.4, 96.7)
PPV, % (95% CI)	13.6 (13.3, 13.9)	8.9 (8.1, 9.7)	19.8 (19.3, 20.3)	30.5 (29.2, 31.9)	19.7 (19.3, 20.2)	47.9 (46.6, 49.3)
NPV, % (95% CI)	99.1 (99, 99.2)	99.4 (99.2, 99.5)	98.4 (98.3, 98.5)	95.2 (94.6, 95.7)	98.3 (98.2, 98.4)	94.6 (94.4, 94.7)
LR+ (95% CI)	1.81 (1.79, 1.82)	3.39 (3.23, 3.55)	2.76 (2.72, 2.8)	2.33 (2.25, 2.42)	2.81 (2.78, 2.85)	10.55 (10.06, 11.06)
LR- (95% CI)	0.11 (0.1, 0.12)	0.22 (0.18, 0.27)	0.18 (0.17, 0.19)	0.27 (0.24, 0.3)	0.2 (0.19, 0.21)	0.66 (0.64, 0.67)
DOR (95% CI)	16.8 (15.13, 18.71)	15.16 (12.06, 19.28)	15.45 (14.17, 16.87)	8.64 (7.58, 9.87)	14.17 (13.24, 15.19)	16.07 (15.12, 17.08)

Abbreviations: CI=confidence interval; TP = true positives; FN = false negatives; FP = false positives, TN = true negatives; NPV=negative predictive value; PPV=positive predictive value. LR=likelihood ratio; DOR=diagnostic odds ratio.

Table 5. Diagnostic test accuracy parameters for algorithm for the diagnosis of de novo chronic heart failure using NT-proBNP level overall and for age subgroups, at the current ESC threshold and at thresholds adjusting for age and high risk, for men only

Test	Rule-in >=125 pg/mL	Rule-in age <50 years >=125 pg/mL	Rule-in age 50-74 years >=250 pg/mL	Rule-in age ≥75 years >=500 pg/mL	Rule-in Age-adjusted	Rule-in High risk >=2000 pg/mL
N	65883	14546	45484	5853	65883	65883
Prevalence, % (95% CI)	11.2 (11, 11.5)	5.1 (4.8, 5.5)	12 (11.7, 12.3)	20.4 (19.4, 21.5)	11.2 (11, 11.5)	11.2 (11, 11.5)
TP, n	6986	627	4868	1039	6534	3042
FN, n	416	122	590	156	868	4360
FP, n	27226	2693	13143	1808	17644	2566
TN, n	31255	11104	26883	2850	40837	55915
Sensitivity, % (95% CI)	94.4 (93.8, 94.9)	83.7 (80.9, 86.3)	89.2 (88.3, 90)	86.9 (84.9, 88.8)	88.3 (87.5, 89)	41.1 (40, 42.2)
Specificity, % (95% CI)	53.4 (53, 53.8)	80.5 (79.8, 81.1)	67.2 (66.7, 67.6)	61.2 (59.8, 62.6)	69.8 (69.5, 70.2)	95.6 (95.4, 95.8)
PPV, % (95% CI)	20.4 (20, 20.9)	18.9 (17.6, 20.3)	27 (26.4, 27.7)	36.5 (34.7, 38.3)	27 (26.5, 27.6)	54.2 (52.9, 55.6)
NPV, % (95% CI)	98.7 (98.6, 98.8)	98.9 (98.7, 99.1)	97.9 (97.7, 98)	94.8 (94, 95.6)	97.9 (97.8, 98.1)	92.8 (92.6, 93)
LR+ (95% CI)	2.03 (2.01, 2.05)	4.29 (4.09, 4.49)	2.72 (2.67, 2.76)	2.24 (2.15, 2.34)	2.93 (2.88, 2.97)	9.37 (8.94, 9.81)
LR- (95% CI)	0.11 (0.1, 0.12)	0.2 (0.17, 0.24)	0.16 (0.15, 0.17)	0.21 (0.18, 0.25)	0.17 (0.16, 0.18)	0.62 (0.6, 0.63)
DOR (95% CI)	19.27 (17.46,21.34)	21.16 (17.42, 25.93)	16.87 (15.46, 18.44)	10.49 (8.8, 12.57)	17.42 (16.2, 18.74)	15.2 (14.3, 16.15)

Abbreviations: CI=confidence interval; TP = true positives; FN = false negatives; FP = false positives, TN = true negatives; NPV=negative predictive value; PPV=positive predictive value. LR=likelihood ratio; DOR=diagnostic odds ratio.

Table 6. Diagnostic test accuracy parameters for algorithm for the diagnosis of de novo heart failure using NT-proBNP level, at the current ESC threshold and at thresholds adjusting for age and high risk and reduced by 25% for people with obesity class I only

Test	Rule-in >=125 pg/ml	Rule-in >=93.75 pg/ml	Rule-in age <50 years >=125 pg/ml	Rule-in age < 50 years >=93.75 pg/ml	Rule-in age 50-75 years >=250 pg/ml	Rule-in age 50-75 years >=187.5 pg/ml	Rule-in age 75 years+ >=500 pg/ml	Rule-in age 75 years+ >=375 pg/ml	Rule-in >=2000 pg/ml	Rule-in >=1500 pg/ml
N	35704	35704	8205	8205	24978	24978	2521	2521	35704	35704
Prevalence, % (95% CI)	8.2 (7.9-8.5)	8.2 (7.9-8.5)	3.5 (3.1-3.9)	3.5 (3.1-3.9)	9 (8.6-9.3)	9 (8.6-9.3)	15.5 (14.1-17)	15.5 (14.1-17)	8.2 (7.9-8.5)	8.2 (7.9-8.5)
TP, n	2722	2784	238	246	1934	2004	312	335	955	1205
FN, n	200	138	49	41	310	240	79	56	1967	1717
FP, n	14596	17656	1601	2237	6407	8202	646	808	798	1265
TN, n	18186	15126	6317	5681	16327	14532	1484	1322	31984	31517
Sensitivity, % (95% CI)	93.2 (92.2-94)	95.3 (94.4-96)	82.9 (78.1-87.1)	85.7 (81.1-89.5)	86.2 (84.7-87.6)	89.3 (88-90.6)	79.8 (75.5-83.7)	85.7 (81.8-89)	32.7 (31-34.4)	41.2 (39.4-43)
Specificity, % (95% CI)	55.5 (54.9-56)	46.1 (45.6-46.7)	79.8 (78.9-80.7)	71.7 (70.7-72.7)	71.8 (71.2-72.4)	63.9 (63.3-64.5)	69.7 (67.7-71.6)	62.1 (60-64.1)	97.6 (97.4-97.7)	96.1 (95.9-96.3)
PPV, % (95% CI)	15.7 (15.2-16.3)	13.6 (13.2-14.1)	12.9 (11.4-14.6)	9.9 (8.8-11.2)	23.2 (22.3-24.1)	19.6 (18.9-20.4)	32.6 (29.6-35.6)	29.3 (26.7-32)	54.5 (52.1-56.8)	48.8 (46.8-50.8)
NPV, % (95% CI)	98.9 (98.8-99.1)	99.1 (98.9-99.2)	99.2 (99-99.4)	99.3 (99-99.5)	98.1 (97.9-98.3)	98.4 (98.2-98.6)	94.9 (93.7-96)	95.9 (94.8-96.9)	94.2 (94-94.5)	94.8 (94.6-95.1)
LR+ (95% CI)	2.09 (2.06-2.13)	1.77 (1.75-1.79)	4.1 (3.83-4.39)	3.03 (2.86-3.22)	3.06 (2.98-3.14)	2.48 (2.42-2.53)	2.63 (2.43-2.85)	2.26 (2.11-2.42)	13.43 (12.32-14.63)	10.69 (9.97-11.45)
LR- (95% CI)	0.12 (0.11-0.14)	0.1 (0.09-0.12)	0.21 (0.17-0.28)	0.2 (0.15-0.26)	0.19 (0.17-0.21)	0.17 (0.15-0.19)	0.29 (0.24-0.35)	0.23 (0.18-0.29)	0.69 (0.67-0.71)	0.61 (0.59-0.63)
DOR (95% CI)	16.94 (14.69-19.65)	17.26 (14.59-20.6)	19.11 (14.11-26.39)	15.18 (11-21.52)	15.89 (14.07-18.01)	14.78 (12.92-16.98)	9.05 (6.99-11.85)	9.76 (7.31-13.25)	19.45 (17.53-21.6)	17.48 (15.94-19.18)

Abbreviations: CI=confidence interval; TP = true positives; FN = false negatives; FP = false positives, TN = true negatives; NPV=negative predictive value; PPV=positive predictive value. LR=likelihood ratio; DOR=diagnostic odds ratio.

Table 7. Diagnostic test accuracy parameters for algorithm for the diagnosis of de novo heart failure using NT-proBNP level, at the current ESC threshold and at thresholds adjusting for age and high risk and reduced by 40%, for people with obesity class II

Test	Rule-in >=125 pg/ml	Rule-in >=87.5 pg/ml	Rule-in age <50 years >=125 pg/ml	Rule-in age <50 years >=87.5 pg/ml	Rule-in age 50-75 years >=250 pg/ml	Rule-in age 50-75 years >=175 pg/ml	Rule-in age 75 years >=500 pg/ml	Rule-in age 75 years >=350 pg/ml	Rule-in >=2000 pg/ml	Rule-in >=1400 pg/ml
N	15966	15966	4814	4814	10490	10490	662	662	15966	15966
Prevalence, % (95% CI)	7.8 (7.4-8.2)	7.8 (7.4-8.2)	4 (3.5-4.6)	4 (3.5-4.6)	9.2 (8.7-9.8)	9.2 (8.7-9.8)	12.8 (10.4-15.6)	12.8 (10.4-15.6)	7.8 (7.4-8.2)	7.8 (7.4-8.2)
TP, n	1133	1179	157	173	803	855	69	74	290	422
FN, n	111	65	35	19	164	112	16	11	954	822
FP, n	5966	7724	978	1446	2518	3485	150	210	284	506
TN, n	8756	6998	3644	3176	7005	6038	427	367	14438	14216
Sensitivity, % (95% CI)	91.1 (89.4-92.6)	94.8 (93.4-95.9)	81.8 (75.6-87)	90.1 (85-93.9)	83 (80.5-85.4)	88.4 (86.2-90.4)	81.2 (71.2-88.8)	87.1 (78-93.4)	23.3 (21-25.8)	33.9 (31.3-36.6)
Specificity, % (95% CI)	59.5 (58.7-60.3)	47.5 (46.7-48.3)	78.8 (77.6-80)	68.7 (67.4-70.1)	73.6 (72.7-74.4)	63.4 (62.4-64.4)	74 (70.2-77.5)	63.6 (59.5-67.5)	98.1 (97.8-98.3)	96.6 (96.3-96.9)
PPV, % (95% CI)	16 (15.1-16.8)	13.2 (12.5-14)	13.8 (11.9-16)	10.7 (9.2-12.3)	24.2 (22.7-25.7)	19.7 (18.5-20.9)	31.5 (25.4-38.1)	26.1 (21-31.6)	50.5 (46.4-54.7)	45.5 (42.2-48.7)
NPV, % (95% CI)	98.7 (98.5-99)	99.1 (98.8-99.3)	99 (98.7-99.3)	99.4 (99.1-99.6)	97.7 (97.3-98)	98.2 (97.8-98.5)	96.4 (94.2-97.9)	97.1 (94.9-98.5)	93.8 (93.4-94.2)	94.5 (94.2-94.9)
LR+ (95% CI)	2.25 (2.19-2.31)	1.81 (1.77-1.84)	3.86 (3.54-4.22)	2.88 (2.7-3.07)	3.14 (3.01-3.28)	2.42 (2.33-2.5)	3.12 (2.63-3.71)	2.39 (2.09-2.74)	12.08 (10.37-14.08)	9.87 (8.79-11.08)
LR- (95% CI)	0.15 (0.13-0.18)	0.11 (0.09-0.14)	0.23 (0.17-0.31)	0.14 (0.09-0.22)	0.23 (0.2-0.27)	0.18 (0.15-0.22)	0.25 (0.16-0.4)	0.2 (0.12-0.35)	0.78 (0.76-0.81)	0.68 (0.66-0.71)
DOR (95% CI)	14.96 (12.33-18.33)	16.39 (12.85-21.3)	16.64 (11.6-24.55)	19.84 (12.63-33.08)	13.61 (11.47-16.25)	13.21 (10.85-16.24)	12.14 (6.99-22.32)	11.58 (6.25-23.63)	15.45 (12.95-18.43)	14.42 (12.44-16.7)

Abbreviations: CI=confidence interval; TP = true positives; FN = false negatives; FP = false positives, TN = true negatives; NPV=negative predictive value; PPV=positive predictive value. LR=likelihood ratio; DOR=diagnostic odds ratio.

Table 8. Diagnostic test accuracy parameters for algorithm for the diagnosis of de novo heart failure using NT-proBNP level, at the current ESC threshold and at thresholds adjusting for age and high risk and reduced by 50%, for people with obesity class III

Test	Rule-in >=125 pg/ml	Rule-in >=75 pg/ml	Rule-in age <50 years >=125 pg/ml	Rule-in age < 50 years >=75 pg/ml	Rule-in age 50 to 74 years >=250 pg/ml	Rule-in age 50 to 74 years >=150 pg/ml	Rule-in age 75 years+ >=500 pg/ml	Rule-in age 75 years+ >=300 pg/ml	Rule-in >=2000 pg/ml	Rule-in >=1200 pg/ml
N	9843	9843	4120	4120	5513	5513	210	210	9843	9843
Prevalence, % (95% CI)	7.7 (7.2-8.3)	7.7 (7.2-8.3)	5 (4.3-5.7)	5 (4.3-5.7)	9.5 (8.7-10.3)	9.5 (8.7-10.3)	15.2 (10.7-20.8)	15.2 (10.7-20.8)	7.7 (7.2-8.3)	7.7 (7.2-8.3)
TP, n	679	718	163	182	428	469	21	23	183	280
FN, n	82	43	42	23	96	55	11	9	578	481
FP, n	3531	5157	993	1700	1311	2085	44	71	123	333
TN, n	5551	3925	2922	2215	3678	2904	134	107	8959	8749
Sensitivity, % (95% CI)	89.2 (86.8-91.3)	94.3 (92.5-95.9)	79.5 (73.3-84.8)	88.8 (83.6-92.8)	81.7 (78.1-84.9)	89.5 (86.6-92)	65.6 (46.8-81.4)	71.9 (53.3-86.3)	24 (21.1-27.2)	36.8 (33.4-40.3)
Specificity, % (95% CI)	61.1 (60.1-62.1)	43.2 (42.2-44.2)	74.6 (73.2-76)	56.6 (55-58.1)	73.7 (72.5-74.9)	58.2 (56.8-59.6)	75.3 (68.3-81.4)	60.1 (52.5-67.4)	98.6 (98.4-98.9)	96.3 (95.9-96.7)
PPV, % (95% CI)	16.1 (15-17.3)	12.2 (11.4-13.1)	14.1 (12.1-16.2)	9.7 (8.4-11.1)	24.6 (22.6-26.7)	18.4 (16.9-19.9)	32.3 (21.2-45.1)	24.5 (16.2-34.4)	59.8 (54.1-65.3)	45.7 (41.7-49.7)
NPV, % (95% CI)	98.5 (98.2-98.8)	98.9 (98.5-99.2)	98.6 (98.1-99)	99 (98.5-99.3)	97.5 (96.9-97.9)	98.1 (97.6-98.6)	92.4 (86.8-96.2)	92.2 (85.8-96.4)	93.9 (93.4-94.4)	94.8 (94.3-95.2)
LR+ (95% CI)	2.29 (2.21-2.38)	1.66 (1.62-1.7)	3.13 (2.87-3.42)	2.04 (1.92-2.17)	3.11 (2.92-3.31)	2.14 (2.05-2.24)	2.65 (1.85-3.8)	1.8 (1.36-2.39)	17.76 (14.3-22.04)	10.03 (8.72-11.55)
LR- (95% CI)	0.18 (0.14-0.22)	0.13 (0.1-0.17)	0.27 (0.21-0.36)	0.2 (0.13-0.29)	0.25 (0.21-0.3)	0.18 (0.14-0.23)	0.46 (0.28-0.74)	0.47 (0.27-0.82)	0.77 (0.74-0.8)	0.66 (0.62-0.69)
DOR (95% CI)	12.99 (10.36-16.52)	12.66 (9.4-17.53)	11.38 (8.12-16.3)	10.24 (6.75-16.31)	12.49 (9.96-15.8)	11.84 (8.99-15.91)	5.72 (2.59-13.31)	3.79 (1.7-9.17)	23.03 (18.08-29.44)	15.28 (12.72-18.37)

Abbreviations: CI=confidence interval; TP = true positives; FN = false negatives; FP = false positives, TN = true negatives; NPV=negative predictive value; PPV=positive predictive value. LR=likelihood ratio; DOR=diagnostic odds ratio.

Table 9. Diagnostic test accuracy parameters for algorithm for the diagnosis of de novo heart failure using NT-proBNP level, at the current ESC threshold and at thresholds adjusting for age and high risk, for people who are at overweight

Test	Rule-in >=125 pg/mL	Rule-in age <50 years >=125 pg/mL	Rule-in age 50-74 years >=250 pg/mL	Rule-in age ≥75 years >=500 pg/mL	Rule-in Age-adjusted	Rule-in High risk >=2000 pg/mL
N	51630	9164	36773	5693	51630	51630
Prevalence, % (95% CI)	9.3 (9, 9.5)	3.3 (3, 3.7)	9.7 (9.4, 10)	16.3 (15.3, 17.3)	9.3 (9, 9.5)	9.3 (9, 9.5)
TP, n	4537	250	3173	772	4195	1905
FN, n	252	54	384	156	594	2884
FP, n	23792	1847	10598	1648	14093	1836
TN, n	23049	7013	22618	3117	32748	45005
Sensitivity, % (95% CI)	94.7 (94.1, 95.4)	82.2 (77.5, 86.4)	89.2 (88.1, 90.2)	83.2 (80.6, 85.5)	87.6 (86.6, 88.5)	39.8 (38.4, 41.2)
Specificity, % (95% CI)	49.2 (48.8, 49.7)	79.2 (78.3, 80)	68.1 (67.6, 68.6)	65.4 (64, 66.8)	69.9 (69.5, 70.3)	96.1 (95.9, 96.3)
PPV, % (95% CI)	16 (15.6, 16.4)	11.9 (10.6, 13.4)	23 (22.3, 23.8)	31.9 (30, 33.8)	22.9 (22.3, 23.6)	50.9 (49.3, 52.5)
NPV, % (95% CI)	98.9 (98.8, 99)	99.2 (99, 99.4)	98.3 (98.2, 98.5)	95.2 (94.4, 95.9)	98.2 (98.1, 98.4)	94 (93.8, 94.2)
LR+ (95% CI)	1.87 (1.84, 1.89)	3.94 (3.69, 4.21)	2.8 (2.74, 2.85)	2.41 (2.29, 2.53)	2.91 (2.86, 2.96)	10.15 (9.59, 10.74)
LR- (95% CI)	0.11 (0.09, 0.12)	0.22 (0.18, 0.29)	0.16 (0.14, 0.17)	0.26 (0.22, 0.3)	0.18 (0.16, 0.19)	0.63 (0.61, 0.64)
DOR (95% CI)	17.43 (15.37, 19.87)	17.53 (13.11, 23.85)	17.63 (15.84, 19.66)	9.35 (7.81, 11.25)	16.41 (15.03, 17.93)	16.19 (15.03, 17.44)

Abbreviations: CI=confidence interval; TP = true positives; FN = false negatives; FP = false positives, TN = true negatives; NPV=negative predictive value; PPV=positive predictive value. LR=likelihood ratio; DOR=diagnostic odds ratio.

Table 10. Diagnostic test accuracy parameters for algorithm for the diagnosis of de novo heart failure using NT-proBNP level, at the current ESC threshold and at thresholds adjusting for age and high risk, for people who are at a healthy weight

Test	Rule-in	Rule-in	Rule-in	Rule-in	Rule-in	Rule-in

	>=125 pg/mL	age <50 years >=125 pg/mL	age 50-74 years >=250 pg/mL	age ≥75 years >=500 pg/mL	Age-adjusted	High risk >=2000 pg/mL
N	33988	5146	23217	5625	33988	33988
Prevalence, % (95% CI)	11.3 (11, 11.6)	3.6 (3.1, 4.1)	11 (10.6, 11.4)	19.4 (18.4, 20.5)	11.3 (11, 11.6)	11.3 (11, 11.6)
TP, n	3734	166	2367	951	3484	1855
FN, n	105	18	195	142	355	1984
FP, n	18144	1263	8247	1875	11385	1884
TN, n	12005	3699	12408	2657	18764	28265
Sensitivity, % (95% CI)	97.3 (96.7, 97.8)	90.2 (85, 94.1)	92.4 (91.3, 93.4)	87 (84.9, 88.9)	90.8 (89.8, 91.7)	48.3 (46.7, 49.9)
Specificity, % (95% CI)	39.8 (39.3, 40.4)	74.5 (73.3, 75.8)	60.1 (59.4, 60.7)	58.6 (57.2, 60.1)	62.2 (61.7, 62.8)	93.8 (93.5, 94)
PPV, % (95% CI)	17.1 (16.6, 17.6)	11.6 (10, 13.4)	22.3 (21.5, 23.1)	33.7 (31.9, 35.4)	23.4 (22.8, 24.1)	49.6 (48, 51.2)
NPV, % (95% CI)	99.1 (99, 99.3)	99.5 (99.2, 99.7)	98.5 (98.2, 98.7)	94.9 (94, 95.7)	98.1 (97.9, 98.3)	93.4 (93.2, 93.7)
LR+ (95% CI)	1.62 (1.6, 1.63)	3.54 (3.31, 3.79)	2.31 (2.27, 2.36)	2.1 (2.02, 2.19)	2.4 (2.36, 2.45)	7.73 (7.32, 8.17)
LR- (95% CI)	0.07 (0.06, 0.08)	0.13 (0.08, 0.2)	0.13 (0.11, 0.15)	0.22 (0.19, 0.26)	0.15 (0.13, 0.16)	0.55 (0.53, 0.57)
DOR (95% CI)	23.49 (19.43, 28.74)	26.78 (16.86, 45.31)	18.25 (15.77, 21.25)	9.48 (7.9, 11.46)	16.17 (14.48, 18.11)	14.02 (12.97, 15.17)

Abbreviations: CI=confidence interval; TP = true positives; FN = false negatives; FP = false positives, TN = true negatives; NPV=negative predictive value; PPV=positive predictive value. LR=likelihood ratio; DOR=diagnostic odds ratio.

Table 11 Diagnostic test accuracy parameters for algorithm for the diagnosis of de novo heart failure using NT-proBNP level, at the current ESC threshold and at thresholds adjusting for age and high risk, for people who are underweight

Test	Rule-in >=125 pg/mL	Rule-in age <50 years >=125 pg/mL	Rule-in age 50-74 years >=250 pg/mL	Rule-in age ≥75 years >=500 pg/mL	Rule-in Age-adjusted	Rule-in High risk >=2000 pg/mL
N	2475	346	1648	481	2475	2475
Prevalence, % (95% CI)	14.3 (13, 15.8)	7.5 (5, 10.8)	13.8 (12.2, 15.6)	21 (17.4, 24.9)	14.3 (13, 15.8)	14.3 (13, 15.8)
TP, n	344	20	218	95	333	169
FN, n	11	6	10	6	22	186
FP, n	1549	151	726	166	1043	168
TN, n	571	169	694	214	1077	1952
Sensitivity, % (95% CI)	96.9 (94.5, 98.4)	76.9 (56.4, 91)	95.6 (92.1, 97.9)	94.1 (87.5, 97.8)	93.8 (90.8, 96.1)	47.6 (42.3, 52.9)
Specificity, % (95% CI)	26.9 (25.1, 28.9)	52.8 (47.2, 58.4)	48.9 (46.2, 51.5)	56.3 (51.2, 61.4)	50.8 (48.7, 53)	92.1 (90.8, 93.2)
PPV, % (95% CI)	18.2 (16.5, 20)	11.7 (7.3, 17.5)	23.1 (20.4, 25.9)	36.4 (30.6, 42.6)	24.2 (22, 26.6)	50.1 (44.7, 55.6)
NPV, % (95% CI)	98.1 (96.6, 99.1)	96.6 (92.7, 98.7)	98.6 (97.4, 99.3)	97.3 (94.2, 99)	98 (97, 98.7)	91.3 (90, 92.5)
LR+ (95% CI)	1.33 (1.28, 1.37)	1.63 (1.28, 2.07)	1.87 (1.76, 1.98)	2.15 (1.9, 2.44)	1.91 (1.81, 2.01)	6.01 (5.01, 7.2)
LR- (95% CI)	0.12 (0.06, 0.21)	0.44 (0.21, 0.89)	0.09 (0.05, 0.16)	0.11 (0.05, 0.23)	0.12 (0.08, 0.18)	0.57 (0.51, 0.63)
DOR (95% CI)	11.36 (6.5, 22.24)	3.65 (1.5, 10.36)	20.5 (11.37, 41.81)	19.83 (9.18, 52.41)	15.51 (10.23, 24.82)	10.54 (8.12, 13.7)

Abbreviations: CI=confidence interval; TP = true positives; FN = false negatives; FP = false positives, TN = true negatives; NPV=negative predictive value; PPV=positive predictive value. LR=likelihood ratio; DOR=diagnostic odds ratio.