The validity of Heart Failure Diagnoses in the Finnish Hospital Discharge Register

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Abstract

Background: Contemporary validation studies of register-based heart failure (HF) diagnoses based on current guidelines and complete clinical data are lacking in Finland and internationally. Our objective was to assess the sensitivity and specificity of HF diagnoses in a nationwide hospital discharge register.

Methods: Using Finnish Hospital Discharge Register data from 2013–2015, we obtained the medical records for 120 patients with a register-based diagnosis for HF (cases) and for 120 in patients with a predisposing condition for HF, but without a HF diagnosis (controls). The medical records of all patients were assessed by a physician who categorized each individual as having HF (with reduced or preserved ejection fraction) or no HF, based on the definition of current European Society of Cardiology HF guidelines. Unclear cases were assessed by a panel of three physicians. This classification was considered as the clinical gold standard, against which the registers were assessed.

Results: Register-based HF diagnoses had a positive predictive value (PPV) of 0.85 (95% CI 0.77-0.91) and a negative predictive value (NPV) of 0.83 (95% CI 0.75-0.90). The PPV decreased when we classified patients with transient HF (duration <6 months), dialysis/lung disease, or HF with preserved ejection fraction as not having HF.

Conclusions: HF diagnoses of the Finnish Hospital Discharge Register have good PPV and NPV, even when patients with pre-existing heart conditions are used as the healthy controls. Our results suggest that HF diagnoses based on register data can be reliably used for research purposes.

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Key Words: Heart failure, validation, sensitivity, specificity, hospital discharge register, drug purchase register, echocardiography

Introduction

Heart failure (HF) is a significant global health problem, with national prevalence estimates varying between 0.12-6.7%. The economic burden of HF on the society is enormous as yearly worldwide costs exceeded 108 billion USD in 2012.[1,2] This is attributed to several factors, including an aging population, nevertheless there remains stimulated interest in identifying risk factors of HF. Administrative registers, such as hospital discharge registers, are an important source of epidemiological data for investigating a wide spectrum of diseases at a population level. To verify data quality, the completeness and validity of the hospital discharge register-based epidemiological data needs to be assessed at regular intervals. Prior validation studies from North America, Netherlands, Denmark, Sweden and the UK have found a relatively low sensitivity and high specificity for HF diagnoses.[3–8,21] A systematic review and meta-analysis reported similar results,[9] with sensitivity and specificity estimates exceeding 69% and 95%, respectively. However, the diverse validation procedures of different studies and patients often render between-study comparisons challenging.[10]

A previous study on the validity of HF diagnoses in the Finnish Hospital Discharge Register demonstrated a specificity of 99.7% with a relatively low sensitivity of 48.5%.[3] However, this study from 2013 was based mainly on the use of brain natriuretic peptide levels for the diagnosis for HF, instead of combining the single marker with detailed clinical data including echocardiography, which is the gold standard to which register-based HF diagnoses should be compared to.[11] The diagnostic techniques of echocardiographic imaging have improved, and it has become an easily available bed side assessment method in clinical practice during the last years. In addition, this previous validation is somewhat outdated as 1) the use of echocardiography in diagnosing HF has increased drastically over the past 10 years; 2) the new European guidelines for diagnosing HF have been introduced[11]; and 3) register-based diagnoses from secondary and tertiary care outpatient clinics were not available at the time.

The aim of the present study was to assess the contemporary validity of the Finnish Hospital Discharge Registers for HF diagnoses. We used full clinical data from both in- and outpatient clinics and adhered to the most recent European Society of Cardiology (ESC) guidelines when assessing the potential presence of clinical HF in patients with a register-based diagnosis.

Materials and Methods

Study Sample and Data Collection

We used data from the Finnish Cardiovascular Disease Register to identify register-based cases and controls. The Finnish Cardiovascular Disease Register[12] contains information on Finnish individuals with a nationwide Hospital Discharge Register-based diagnosis of coronary heart disease, stroke, or heart failure after the year 1994. We chose a sample size of 120 cases and controls as this provided a statistical power of 0.80, 0.93, and 0.99 for specificity and sensitivity when specificity was set at 0.8, 0.9, and 0.95.[13] We randomly drew 120 patients with a first hospital discharge register -based diagnosis of HF (cases) and another 120 patients with a first register-based diagnosis of a cardiac condition predisposing to HF from the Finnish Hospital Discharge Register[14], but without a diagnosis of HF (controls). These first diagnoses occurred between 2013 and 2015. **After identifying these individuals, we then applied and received permission from the two Hospital Districts' chiefs of medicine and/or research to access relevant electronic health records of these individuals.** Sixty patients with and without HF were drawn from secondary and tertiary care patients of the (i) Finland Proper and (ii) Central Finland Health Care Districts, for a total of 240 patients. **We excluded patients with a first diagnosis at age under 30 or over 80 years to avoid the possible confounding effects of substance use in the young and multimorbidity in the elderly.**

Hospital Discharge Register

The National Institute for Health and Welfare maintains a nationwide hospital discharge register that covers information on all hospitalizations in Finland after 1967.[14] **Outpatient diagnoses from secondary and tertiary care are available since 1998. In this study, we used data from in- and outpatient care diagnoses from secondary and tertiary care to define register-based cases and controls.** The hospital discharge register includes data on admission and discharge

dates, performed procedures, and up to four different diagnoses for each discharge, coded in our study period with ICD-10 (International Classification of Diseases, 10th Revision).[15]

Definition of Register-Based HF (i.e., Cases) and Register-Based Other Cardiac Disease without HF (i.e., Controls)

Patients with ICD-10 codes I50, I110, I130, or I132 in the hospital discharge register for the first admission were defined as having register-based HF (cases). **Main and secondary diagnoses from secondary and tertiary care for inpatient and outpatient admissions were accepted.** Patients with a diagnostic ICD-10 code for a condition predisposing to HF, i.e., coronary heart disease (I20-25 or coronary revascularization), cardiomyopathy (I42), or valvular heart disease (I34-I37) in the hospital discharge register without a diagnosis for HF were defined as controls.

Diagnosis of HF Based on Clinical Assessment

We used a modified diagnostic algorithm based on the ESC Acute and Chronic Heart Failure Guidelines from 2016 as the definition of clinical HF (**Figure 1**).[11] Based on this algorithm, all hospital discharge register -based cases and controls were categorized as having: 1) HF with reduced ejection fraction (HFrEF); 2) HF with preserved ejection fraction (HFpEF); 3) HF based on clinical criteria if no echocardiography was available; and 4) no HF. **The same algorithm was used for both cases and controls.** The diagnostic procedure in depth and additional details are reported in the **Supplemental Methods**. The ESC guidelines also include a definition of HF with mildly reduced ejection fraction (HFmrEF). In this study, we classified these patients as having HFpEF.

The Validation Procedure

An internist examined all relevant electronic hospital patient records prior to, and for 6 months after, the register-based index date for information related to HF (Supplemental Table). Information on history of risk factors for HF was also collected (**Supplemental Table**), although it was not used as a part of our algorithm. **The register-based diagnoses were based**

on an in- or outpatient visit to secondary or tertiary care. We used the electronic patient records to review all relevant patient charts, echocardiography reports, laboratory tests, ECGs, and radiology reports for relevant information (**Supplemental Table**). **Patient records were available from all secondary and tertiary care public sector hospitals from both regions, and were available for all study patients.** All uncertain and borderline cases were reviewed by a panel of two internists (T.N. and M.V.) and one cardiologist (J.L.), and diagnosis was based on consensus.

Sensitivity Analyses

In addition to the main analyses in which all patients with HFpEF, HFrEF, and clinical HF were considered as having HF, we also performed sensitivity analyses with three alternative definitions of HF. First, we considered only cases of chronic HF and excluded those with transient HF (resolving of signs and symptoms and normalization of ejection fraction within six months). Second, we classified patients on dialysis or with chronic hypoxemic pulmonary conditions (**Supplemental Table**) as not having HF, as these patients had almost always congestive findings. Third, we considered only patients with HFrEF as having HF.

Additional Assessment of Validity of HF Diagnoses Based on Furosemide Purchases

Every prescription drug purchase in Finland is stored in the nationwide Prescribed Drug Purchase Register.[16] **We also assessed the validity of HF diagnoses that were based solely on repeated furosemide purchases. Because furosemide purchase data were not available for individuals included in the Finnish Cardiovascular Disease Register, we used information from 75 081 participants who took part in nationwide FINRISK population surveys between 1972 and 2012.[17]** Of these individuals, we identified 2 967 30-80-year-old persons who had purchased furosemide and/or furosemide combined with a potassium sparing diuretic (ATC codes C03CA01 and C03EB01) three or more times. **All FINRISK participants have given consent to use their yearly-collected register data for research purposes.** We then assessed the proportion of persons that developed a hospital discharge register -based diagnosis of HF (defined

above) or hepatic or renal insufficiency over three- and five-year follow-up periods. Additional details are reported in the **Supplemental Methods**.

Statistical methods

We compared characteristics of patients with and without a register-based diagnosis of HF using regular ANOVA with equal variance assumption for continuous variables and chi-squared tests with continuity correction for categorical variables, with means and standard deviations provided with p-values. **We calculated the positive and negative predictive values (PPV, NPV) and positive and negative likelihood ratios (PLR, NLR) for the hospital discharge register for diagnosing clinical HF along with 95% confidence intervals.**[18] In addition, we assessed the agreement between register-based and clinical diagnoses of HF using Cohen's kappa statistic. All statistical analyses were performed using R v.3.5.0.

Results

Characteristics of the study sample are presented in **Table 1**. Out of 240 patients, 76 were women (31.7%). The mean age of the whole sample was 64.8 (SD 8.9) years. **Despite a lack of matching, the age- and sex-distributions of the cases and controls were similar.** The most common comorbidities were coronary heart disease (150 patients, 64.1%) and hypertension (145 patients, 60.7%). The echocardiographical coverage of our sample was good, with 199 (82.9%) of patients having echocardiographic data available. The indices on diastolic dysfunction were available for only 27% during the given study period (**Table 1**). The mean ejection fraction was 40.4 (SD 16) % in the register-based HF group and 56.2 (SD 12.1) % in the group without register-based HF diagnosis. In total, our physician committee reviewed 41 unclear cases (17.1%).

We observed 20 false negative cases (16.7%) in the control group and 18 false positive cases (15.0%) (**Table 2**). The most common reasons for a false positive diagnosis were dyspnoea (6 patients) and fluid retention (3 patients) due to reasons other than HF. The reasons for false negative diagnoses were the use of only the ICD-code of the underlying cause of HF (9 patients), a missed diagnosis (6 patients), or a properly coded HF diagnosis in the patient records that was not transmitted to the Finnish Hospital Discharge Register (5 patients**). In the main analysis, register-based diagnoses had a positive predictive value of 0.85 (95% CI 0.77-0.91) and a negative predictive value of 0.83 (95% CI 0.75-0.90) for HF. Positive likelihood ratio was 5.48 for all cases of HF.** The scatterplot of peak proBNP versus lowest ejection fraction in groups by HF status is depicted in **Figure 2**.

When HF was defined as only chronic HF, PPV fell to 0.63 (0.54-0.72) but NPV improved slightly to 0.88 (0.80-0.93), and positive likelihood ratio was also lower at 2.83 (2.17-3.68) (Table 2). Excluding chronic obstructive pulmonary disease and dialysis patients from HF patients lowered PPV slightly to 0.82 (0.75-0.89) and NPV to 0.83 (0.75-0.90) compared with the main definition, but PLR improved to 4.79 (3.22-7.13). When HF was defined strictly as

only HFrEF, this resulted in a significantly poorer PPV of 0.44 (0.35-0.54), but an improved NPV of 0.91 (0.84, 0.95).

The prognosis of individuals who received a tentative diagnosis based on repeated furosemide purchases is shown in **Table 3**. A total of 2477 individuals had data available for a 3-year-follow up after receiving a tentative diagnosis and 2059 individuals had data for a full 5-year-follow up. Of these persons, 1024 (41.3%) and 1054 (51.2%) were diagnosed with HF during the follow up, respectively. Lone HF (without hepatic or renal insufficiencies) was the only diagnosis in 885 (35.7%) and 903 (43.9%) patients in 3-year and 5-year follow-up groups, respectively. A notable number of individuals used furosemide without any register-based diagnosis for HF, renal insufficiency or hepatic insufficiency, 1189 (48.0%) and 808 (39.2%) in 3-year and 5-year follow-up groups.

Discussion

In this study, we validated the HF diagnoses of the Finnish Hospital Discharge Register that occurred in 2013–2015. **Even when using patients with pre-existing heart conditions as the controls, we observed a positive predictive value of 0.85 and a negative predictive value of 0.83 for HF. Comparing to a gold standard test, the ESC guideline, for HF diagnosis with a PPV of 1.0, this study showed that the Finnish Hospital Discharge Register has a high predictive value for discriminating HF cases from non-cases correctly even if individuals with prevalent heart disease were used as the controls.**

The previous Finnish Hospital Discharge Register validation study of HF by Mähönen et al. reported a high specificity of 99.7% and a moderate sensitivity of 48.5%.[3] **As prevalence of HF in the general population affects these measures, we chose to include only the predictive values and likelihood ratios.** The contrast between our current findings and the previous study[3] from Finland may be explained by several factors. First, the sample of the prior study was drawn from population survey participants increasing its sensitivity whereas in our study, both cases and controls were secondary or tertiary care patients. Another key difference is that previous study used brain natriuretic peptide levels without a thorough cardiovascular clinical examination or echocardiography data, which may have explained to a lower observed sensitivity.[19,20] **Other alternative definitions with stricter criteria for HF lead to improved NPV and lower PPV in our validation study, as was expected.**

Previous validation studies for register-based cardiovascular disease diagnoses have been performed also in Sweden, Denmark, United Kingdom, and the Netherlands.[4-8,21] Ingelsson et al. reviewed the validity of 321 HF register-based diagnoses observed in a population cohort of 2322 middle-aged Swedish men.[4] The validity of these diagnoses was 82% in all cases, with echocardiographic examinations increasing the validity to 88%. In patients who were treated at internal medicine or cardiology clinics, the respective validities were 86% and 91%.[4] **These**

validity estimates correspond to the predictive values observed in our study, although direct comparisons are not possible as Ingelsson et al. did not compare HF cases with non-cases. Kümler et al. examined all patients who were hospitalized during a 12-month-period due to any cause in a single hospital in Denmark and observed a specificity of 99% and sensitivity of 29% for all patients and concluded that HF is severely underreported in the Danish hospitalized patients.[7] Delekta et al. validated HF diagnoses by reviewing 500 patient records in northern Denmark from 2007 and reported a positive predictive value of 83.6% (95% CI: 80.1-86.7%) for definite and probable HF.[8] Khand et al. performed a comparable study with similar findings in Glasgow, using a cohort of AF patients as a control group.[21] The authors concluded that the use of hospital discharge codes substantially underestimates hospital events related to HF in the United Kingdom, as 54% of AF cases with true HF did not receive a discharge code for HF during a 3-month follow-up period. In Maastricht, the Netherlands, Merry et al. performed a study of hospital discharge register diagnoses by validating hospital discharge register diagnoses of coronary heart disease, acute myocardial infarction, unstable angina pectoris, and HF against diagnoses from the cardiovascular disease register of the Maastricht cohort study.[5] The authors reported a low sensitivity of 43% and a positive predictive value of 0.80 for HF. In addition, a previous meta-analysis concluded that the specificity of hospital discharge registers is high for HF (>90%), but sensitivity is usually much lower (≥69%).[9] Based on available HF validation studies, hospital discharge registers tend to underestimate the number of hospitalizations for HF with substantial differences between countries.[3-9] **However, direct head-to-head comparisons between the national hospital discharge registers of various countries have not been performed, as individual-level data would be best suited for this. This is also the reason why most studies report different epidemiological measures.**

The main reasons for the differing results of prior national studies are due to the highly variable study settings, i.e., differences in study samples and diagnostic criteria. Additionally, the diagnosis of HF can often be challenging.[11] Chronic, stable HFpEF remains a difficult entity to diagnose even for an experienced physician. The assessment of diastolic dysfunction and diagnosis of HFpEF

have also been a subject of change recently, as technological and diagnostic progress has made it possible to more precisely diagnose also these patients – however, the diastolic indices were available for only a minority (27%) of patients in our study as well. Additionally, infections, renal failure, or chronic obstructive pulmonary disease exacerbation, etc., can present with HF-like symptoms such as breathlessness, cough, reduced exercise tolerance, and peripheral swelling or weight gain which all may be difficult to differentiate from common HF symptoms. Secondly, there may be various coexisting disease symptoms at the same time.[22] When another parallel disease process triggers an episode of decompensation in patients with a prior diagnosis of chronic HF, sometimes only the underlying cause for HF may have been coded in the hospital discharge register. In our study, this occurred quite commonly with decompensations triggered by acute myocardial infarctions. In addition, mild or asymptomatic HF events can more often be left uncoded compared to HF patients with active, recurring disease. One challenge of the Finnish Hospital Discharge Register is that it relies on ICD-10 coding which does not differentiate between acute and chronic HF which are different clinical entities.[23] The use of ICD-11 or ICD-10-CM (Clinical Modification) could be beneficial as these medical classifications have a wide spectrum of HF diagnosis codes available, including acute, chronic, and acute-on-chronic HF.

A recent article by Cainzos-Achirica et al. (2018) reviewed the many challenges of evaluating chronic and acute HF events in large health care databases.[10] For the gold standard diagnosis, they recommended the 2016 ESC guideline criteria jointly with BNP levels, cardiac imaging, and echocardiographic data, highlighting the need of a documented structural abnormality for the development and diagnosis of HF.[11] Unfortunately, diagnosing chronic HF is often more difficult than diagnosing acute HF, because cardiac structural abnormalities may asymptomatically precede the clinical syndrome[24] in contrast to a more clearly manifesting onset with an acute myocardial injury.[25,26] In most cases the structural abnormalities related to HF are permanent, whereas HF symptoms may occur periodically as the failing heart leads to many phases of acute decompensations before chronic HF. In validation studies, however, the study period may overlap with any of the aforementioned parts: the asymptomatic compensated structural abnormality stage,

a clinical decompensation period, or a chronic stable or unstable stage later in the disease progression.[10]

In addition to assessing the validity of hospital discharge register-based diagnoses for HF, we also assessed if the Finnish Prescribed Drug Register data could be used to reliable diagnose HF. Previous clinical data of these patients have been lacking, and we observed that approximately half of the individuals with repeated furosemide purchases did not receive a hospital discharge register-based diagnosis for HF, liver disease or renal insufficiency over a 5-year follow-up. It is conceivable that furosemide is quite commonly prescribed by primary care doctors as a potential therapy for lower extremity swelling from any cause, even in spite of clinical and research evidence against the use of furosemide for venous insufficiency.[27] We therefore conclude that although furosemide use can be most likely used to increase sensitivity of register-based HF diagnoses, it leads to decreased specificity.

We tried to address many of the shortcomings of prior validation studies.[10] Indeed, we used the ESC diagnostic algorithm for HF as the gold standard and included a control group, thus enabling us to perform different analyses for alternative definitions of HF. We adhered to the STARD initiative for reporting all measures as described by the initiative.[29] As a study limitation, the HF patients were not classified as having possible, probable, or definite HF to facilitate interpretation of our results.[5,21] **In addition, echocardiography and proBNP levels were not accessible for all patients, and we did not have access to primary care data (including furosemide usage data) where follow-up visits sometimes occurred.** However, data may not be completely reliable as echocardiography is rarely performed at local health care centres. For unclear cases, we used an alternative approach, a panel of physicians to review the clinical data to reach consensus. In general, echocardiographic data and its quality is highly dependent on the individual investigators and hospital protocols, and especially the diastolic parameters aren't even measured in many hospital protocols yet, so we couldn't use register data to fully evaluate the distinction between definitive noncardiac congestion and HFpEF. Right-side catheterization or other invasive

stress tests for precise cardiopulmonary assessment would have been optimal for this[28], but unfortunately no testing had been done to any of our study patients either. Indeed, in real-world clinical practice, the detailed evaluation of diastolic function is not often performed for patients with HF symptoms during the hospital admission.

We conclude that the Finnish Hospital Discharge Register reliably discriminates between HF cases and noncases, better with acute cases than with chronic ones, even if individuals with prevalent heart disease were used as the controls. However, the predictive values of HF diagnosed could be further improved through proper coding of also mild and chronic HF cases and reduction of clerical errors which lead to improper coding. Additional diagnostic codes not present in ICD-10, such as acute, acute-on-chronic and chronic HF are also needed. All clinicians in countries with nationwide health care registers should become increasingly aware of the clinical and research benefits of a structurally unified register and its coding system. Treating physicians should pay attention to correct coding of all diagnoses during patient encounters, as high-quality register data benefit both the clinician and the researcher.

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Conflicts of interest

VS has participated in a conference trip sponsored by Novo Nordisk and received a honorarium from the same source for participating in an advisory board meeting. He also has research collaboration with Bayer ltd.

Authors' contributions

MV: Contributed to design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AP: Contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JL: Contributed to conception and design; contributed to interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AH: Contributed to design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy

MK: Contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

TJ: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript;critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy

VS: Contributed to design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

References

1. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev*. 2017;3(1):7-11. doi:10.15420/cfr.2016:25:2
2. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol*. 2014;171(3):368-376. doi:10.1016/j.ijcard.2013.12.028
3. Mähönen M, Jula A, Harald K, et al. The validity of heart failure diagnoses obtained from administrative registers. *Eur J Prev Cardiol*. 2013;20(2):254-259. doi:10.1177/2047487312438979
4. Ingelsson E, Ärnlöv J, Sundström J, Lind L. The validity of a diagnosis of heart failure in a hospital discharge register. *Eur J Heart Fail*. 2005;7(5):787-791. doi:10.1016/j.ejheart.2004.12.007
5. Merry AHH, Boer JMA, Schouten LJ, et al. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in the Netherlands using the cardiovascular registry Maastricht cohort study. *Eur J Epidemiol*. 2009;24(5):237-247. doi:10.1007/s10654-009-9335-x
6. Mard S, Nielsen FE. Positive predictive value and impact of misdiagnosis of a heart failure diagnosis in administrative registers among patients admitted to a University Hospital cardiac care unit. *Clin Epidemiol*. 2010;2(1):235-239. doi:10.2147/CLEP.S12457
7. Kümler T, Gislason GH, Kirk V, et al. Accuracy of a heart failure diagnosis in administrative registers. *Eur J Heart Fail*. 2008;10(7):658-660. doi:10.1016/j.ejheart.2008.05.006
8. Delekta J, Hansen SM, AlZuhairi KS, Bork CS, Joensen AM. The validity of the diagnosis of heart failure (I50.0-I50.9) in the Danish National Patient Register. Dan Med J. 2018 Apr;65(4). pii: A5470.
9. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: A systematic review and meta-analysis. *PLoS One*. 2014;9(8). doi:10.1371/journal.pone.0104519
10. Cainzos-Achirica M, Rebordosa C, Vela E, et al. Challenges of Evaluating Chronic Heart

Failure and Acute Heart Failure Events in Research Studies Using Large Healthcare Databases. *Am Heart J*. 2018;202:76-83. doi:10.1016/J.AHJ.2018.05.005

11. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail*. 2016;18(8):891-975. doi:10.1002/ejhf.592
12. Kiviniemi TO, Pietilä A, Gunn JM, Aittokallio JM, Mähönen MS, Salomaa VV, Niiranen TJ. Trends in rates, patient selection and prognosis of coronary revascularisations in Finland between 1994 and 2013: the CVDR. EuroIntervention. 2016;12(9):1117-1125.
13. Flahault A, Cadilhac M, and Thomas G. Sample size calculation should be performed for design accuracy in diagnostic test studies. Journal of Clinical Epidemiology, 2005;58(8):859-862
14. Sund R, Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health. 2012 Aug;40(6):505-15. doi: 10.1177/1403494812456637
15. WHO, International Classification of Diseases, 10th Revision. http://apps.who.int/classifications/icd10/browse/2016/en
16. KELA (Social Security Institution of Finland), Statistics on reimbursements for prescription medicines. https://www.kela.fi/web/en/492
17. Borodulin K, Vartiainen E, Peltonen M. Forty-year trends in cardiovascular risk factors in Finland. Eur J Public Health. 2015 Jun;25(3):539-46. doi: 10.1093/eurpub/cku174
18. Šimundić A-M. Measures of Diagnostic Accuracy: Basic Definitions. EJIFCC vol. 19,4 203-11. 20 Jan. 2009
19. Anjan VY, Loftus TM, Burke MA, et al. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. Am J Cardiol 2012;110:870-876
20. Bishu K, Deswal A, Chen HH, et al. Biomarkers in acutely decompensated heart failure with preserved or reduced ejection fraction. Am Heart J 2012;164:763-770.e3
21. Khand AU, Shaw M, Gemmel I, Cleland JG, Do discharge codes underestimate

hospitalisation due to heart failure? Validation study of hospital discharge coding for heart failure. Eur J Heart Fail. 2005 Aug;7(5):792-7.

22. Campbell RT, McMurray JJ, Comorbidities and differential diagnosis in heart failure with preserved ejection fraction. Heart Fail Clin. 2014 Jul;10(3):481-501. doi: 10.1016/j.hfc.2014.04.009.

23. Frolova N, Bakal JA, McAlister FA, Assessing the use of international classification of diseases-10th revision codes from the emergency department for the identification of acute heart failure. JACC Heart Fail. 2015 May;3(5):386-391. doi: 10.1016/j.jchf.2014.11.010.

24. Heinzel FR, Hohendanner F, Jin G, Myocardial hypertrophy and its role in heart failure with preserved ejection fraction. J Appl Physiol (1985). 2015 Nov 15;119(10):1233-42. doi: 10.1152/japplphysiol.00374.2015. Epub 2015 Jul 16.

25. Pfeffer MA, Braunwald E, Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. Circulation. 1990;81:1161–1172.

26. Zornoff LAM, Paiva SAR, Duarte DR, et al. Ventricular remodeling after myocardial infarction: concepts and clinical implications. Arq Bras Cardiol. 2009;92:157–164.

27. Rathbun SW, Kirkpatrick AC, Treatment of chronic venous insufficiency. Curr Treat Options Cardiovasc Med. 2007 Apr;9(2):115-26.

28. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Fail. 2010;3:588–595. doi: 10.1161

29. Benchimol, E. I., et al."Development and use of reporting guidelines for assessing the quality of validation studies of health administrative data. J Clin Epidemiol 64(8): 821-829.

Figure Legends

Figure 1. Diagnostic algorithm adapted from the ESC heart failure guidelines 2016. Abbreviations: HF, Heart failure of any kind; EF, ejection fraction; proBNP, N-terminal pro b-type natriuretic peptide; ALI-ARDS, acute lung injury and adult respiratory distress syndrome; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

Figure 2. Scatterplot of brain natriuretic peptides and cardiac ejection fraction in patients classified by heart failure status (N=147 with data available). Abbreviations: proBNP, Brain natriuretic peptide levels; HF, Heart failure.

Table 1. Study sample characteristics.

Characteristic	N with data	Overall	No register-based HF	Register-based HF	P value
N	240	240	120	120	
Women	240	76 (31.7)	38 (31.7)	38 (31.7)	0.99
Age, mean (SD)	240	64.83 (8.9)	64.30 (8.6)	65.35 (9.2)	0.36
Medical History					
Coronary artery disease	234	150 (64.1)	94 (79.0)	56 (48.7)	<0.001
Arrhythmia	238	86 (36.1)	23 (19.5)	63 (52.5)	<0.001
Hypertension	239	145 (60.7)	70 (58.8)	75 (62.5)	0.65
Perimyocarditis	240	4 (1.7)	3 (2.5)	1 (0.8)	0.61
Cardiomyopathy	240	25 (10.4)	2 (1.7)	23 (19.2)	<0.001
Diabetes mellitus	240	85 (35.4)	33 (27.5)	52 (43.3)	0.015
Inflammatory heart disease	240	3 (1.2)	1 (0.8)	2 (1.7)	0.99
Dialysis	240	3 (1.2)	1 (0.8)	2 (1.7)	0.99
Cardiac metastases	240	5 (2.1)	0 (0.0)	5 (4.2)	0.07
Severe lung disease	240	5 (2.1)	0 (0.0)	5 (4.2)	0.07
Any symptom of HF	239	158 (66.1)	49 (41.2)	109 (90.8)	<0.001
Any sign of HF	235	100 (42.6)	18 (15.1)	82 (70.7)	<0.001
Pulmonary edema	225	19 (8.8)	2 (2.0)	17 (14.5)	<0.001
Highest proBNP, mean (SD)	164	5822 (8841)	2583 (5297)	7502 (9813)	0.001
Echocardiography					
Lowest EF, mean (SD)	199	47.6 (16.4)	56.2 (12.1)	40.4(16.1)	<0.001
Diastolic dysfunction	64	41 (64.1)	14 (45.2)	27 (81.8)	0.005
Structural abnormality	176	161 (91.5)	67 (85.9)	94 (95.9)	0.04
Clinical Diagnosis					
HFrEF	240	64 (26.7)	11 (9.2)	53 (44.2)	<0.001
HFpEF	240	51 (21.2)	8 (6.7)	43 (35.8)	<0.001
Clinical HF	240	7 (2.9)	1 (0.8)	6 (5.0)	<0.001
No HF	240	118 (49.2)	100 (83.3)	18 (15.0)	<0.001
Transient HF	240	34 (14.2)	6 (5.0)	28 (23.3)	<0.001
Chart review by three MDs	240	41 (17.1)	12 (10.0)	29 (24.2)	0.006

Numbers are presented as n (%) unless otherwise indicated.
Abbreviations: EF, ejection fraction; HF, Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; HFpEF, Heart Failure with preserved Ejection Fraction; proBNP, N-terminal pro b-type natriuretic peptide.

Table 2. Agreement between clinical and register-based diagnoses with varying criteria for clinical diagnosis.

	Definition of positive clinical diagnosis							
	Main analysis		Sensitivity analyses					
	Chronic and transient (<6 months) HF		Chronic HF		Chronic and transient (<6 months) HF (excluding dialysis and lung patients)		Chronic and transient HFrEF	
Register-based HF diagnosis	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Positive	102	18	76	44	99	21	53	67
Negative	20	100	15	105	20	100	11	109
Measure								
PPV	0.85 (0.77, 0.91)		0.63 (0.54, 0.72)		0.82 (0.75, 0.89)		0.44 (0.35, 0.54)	
NPV	0.83 (0.75, 0.90)		0.88 (0.80, 0.93)		0.83 (0.75, 0.90)		0.91 (0.84, 0.95)	
PLR	5.48 (3.56, 8.45)		2.83 (2.17, 3.68)		4.79 (3.22, 7.13)		2.18 (1.75, 2.71)	
NLR	0.19 (0.13, 0.29)		0.23 (0.15, 0.38)		0.20 (0.14, 0.31)		0.28 (0.16, 0.48)	
Kappa	0.68 (0.56, 0.81)		0.50 (0.39, 0.63)		0.66 (0.53, 0.78)		0.35 (0.24, 0.46)	
Accuracy	0.84 (0.79, 0.89)		0.75 (0.69, 0.81)		0.83 (0.78, 0.87)		0.68 (0.61, 0.73)	

Abbreviations: HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction.

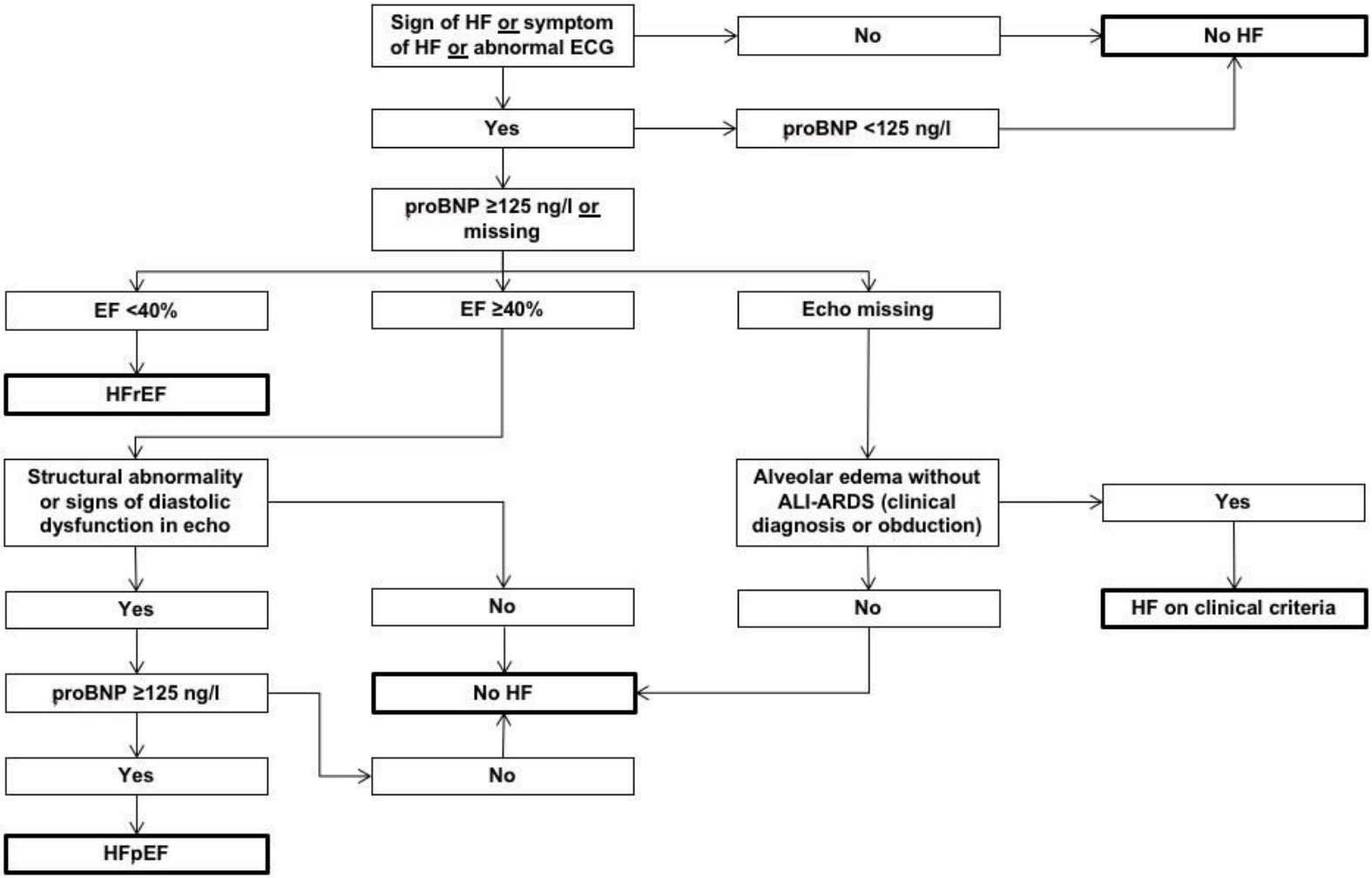
Measures: PPV, Positive Predictive Value – the probability of having HF in a subject with a register-based diagnosis; NPV, Negative Predictive Value – the probability of not having HF in a subject without a register-based diagnosis for HF; PLR, Positive likelihood ratio – ratio of a positive result in subjects with HF to the subjects without HF; NLR, Negative likelihood ratio – ratio of a negative result in subjects with HF to the subjects without HF; Kappa – The proportion of responses in which the two (positive or negative) responses agree.

Table 3. Three- and five-year prognosis of individuals with an initial furosemide-purchase -based diagnosis of heart failure.

Register-based diagnoses of HF, CKD and liver disease after repeated furosemide purchases	3-year follow-up (N=2477)	5-year follow-up (N=2059)
No HF	1453 (58.7)	1005 (48.8)
No diagnoses for HF, CKD, or liver disease	1189 (48.0)	808 (39.2)
CKD	210 (8.5)	160 (7.8)
Liver disease	42 (1.7)	31 (1.5)
CKD and liver disease	12 (0.4)	6 (0.3)
HF	1024 (41.3)	1054 (51.2)
HF as only diagnosis	885 (35.7)	903 (43.9)
HF and CKD	112 (4.5)	120 (5.8)
HF and liver disease	20 (0.8)	20 (1.0)
HF, CKD and liver Disease	7 (0.3)	11 (0.5)

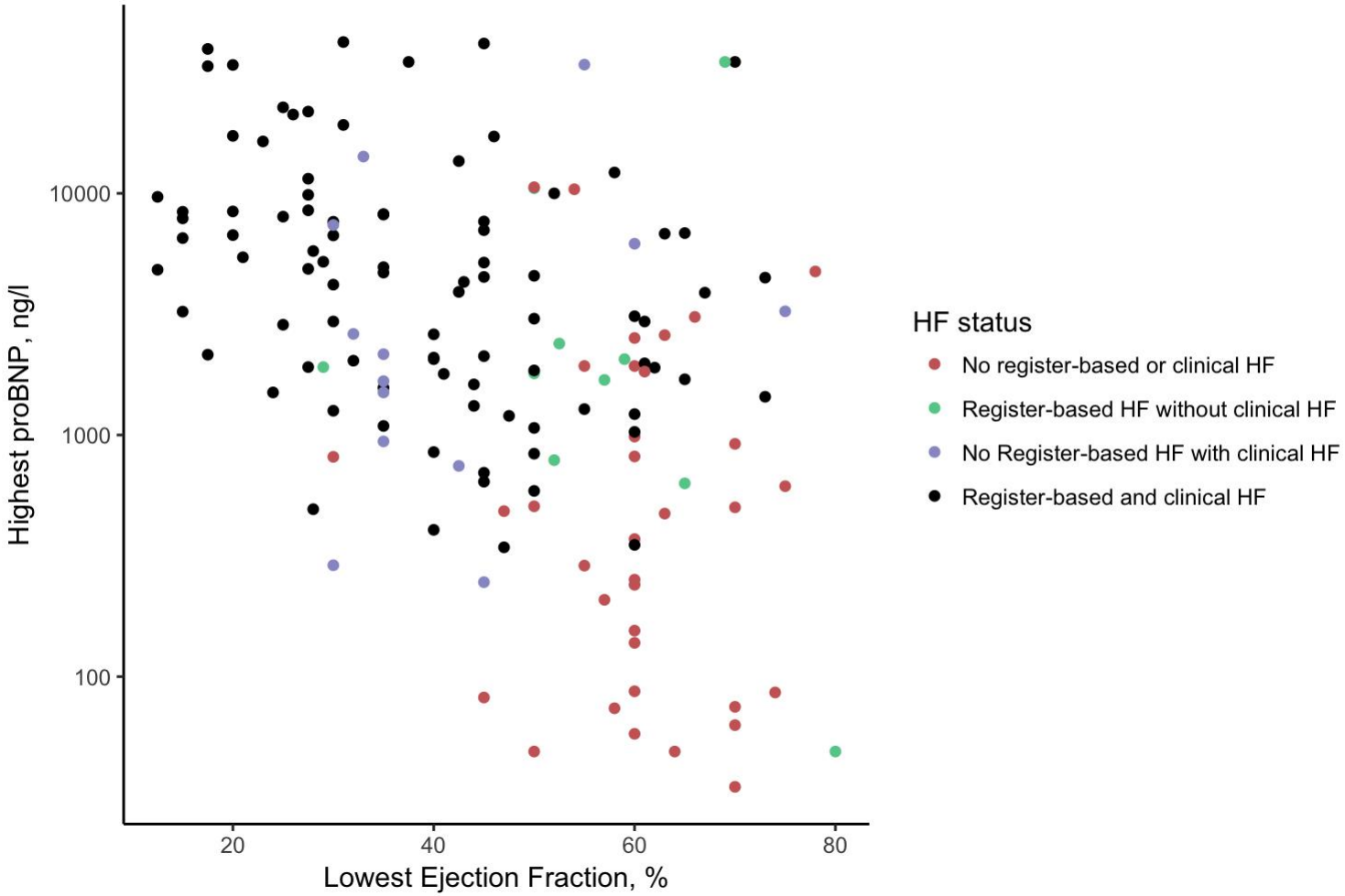
Abbreviations: HF, Heart failure; CKD, Chronic kidney disease.

Figure 1. Diagnostic algorithm adapted from the ESC heart failure guidelines 2016.



Abbreviations: HF, Heart failure of any kind; EF, ejection fraction; proBNP, N-terminal pro b-type natriuretic peptide; ALI-ARDS, acute lung injury and adult respiratory distress syndrome; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

Figure 2. Scatterplot of brain natriuretic peptides and cardiac ejection fraction in patients classified by heart failure status (N=147 with data available).



Abbreviations: proBNP, Brain natriuretic peptide levels; HF, Heart failure.