Misdiagnosis of Heart Failure: A Systematic Review of the Literature

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ABSTRACT

Background: Heart failure (HF) is a chronic disease associated with a significant burden to patients, families, and health services. The diagnosis of HF can be easily missed owing to similar symptoms with other conditions especially respiratory diseases.

Methods and Results: We conducted a systematic review to determine the rates of HF and cardiomyopathy misdiagnosis and explored the potential causes. The included studies were narratively synthesized. Ten studies were identified including a total of 223,859 patients. There was a lack of definition of HF misdiagnosis in the studies and inconsistent diagnostic criteria were used. The rates of HF misdiagnosis ranged from 16.1% in hospital setting to 68.5% when general practitioner referred patients to specialist setting. The most common cause for misdiagnosis was chronic obstructive pulmonary disease (COPD). One study using a COPD cohort showed that HF was unrecognized in 20.5% of patients and 8.1% had misdiagnosis of HF as COPD. Another study suggests that anemia and chronic kidney disease are associated with an increase in the odds of unrecognized left ventricular systolic dysfunction. Other comorbidities such as obesity, old age, atrial fibrillation, and ischemic heart disease are prevalent in patients with a misdiagnosis of HF.

Conclusions: The misdiagnosis of HF is an unfortunate part of everyday clinical practice that occurs with a variable rate depending on the population studied. HF is frequently misdiagnosed as COPD. More research is needed to better understand the missed opportunities to correctly diagnose HF so that harm to patients can be avoided and effective treatments can be implemented. (*J Cardiac Fail 2021;27:925−933*)

Key Words: Heart failure, diagnosis, misdiagnosis, systematic review.

Heart failure (HF) is a global problem responsible for considerable morbidity and mortality.[1] There are an estimated 64.34 million patients[2] with HF globally, with the 5-year mortality as high as 43.3%.[3] Decades of research in HF with reduced ejection fraction treatments have culminated in a significant evidence base to support many medical therapies and devices that improve the survival and quality of life for HF patients.[3] However, providing treatments, hospitalizations, and community care for patients with HF results in a significant cost to health service.[4,5] Although there have been some improvements in diagnostics in the form of natriuretic peptide testing, echocardiography, and cardiac magnetic resonance imaging, an area that requires further understanding is whether patients who are found to have HF actually had missed opportunities for earlier diagnosis.[6]

HF is a clinical syndrome characterized by dyspnea, orthopnea, peripheral edema, and clinical signs of congestion, which can be mistaken for other conditions especially in the early stages. Studies have reported that respiratory diseases, especially chronic obstructive pulmonary disease (COPD), and other comorbidities including myocardial ischemia, atrial fibrillation, obesity, deconditioning and old age to be common causes of HF misdiagnosis.[6−11] These comorbidities cause dyspnea and decreased exercise tolerance, which are often the main symptoms of HF. In addition, the early recognition of HF in the ambulatory setting is challenging because the disease often progresses slowly with only subtle signs or symptoms leading to delay or initial missed diagnosis.[6] Registry data indicate that 80% of HF diagnoses are made in hospital, despite 40% of patients having symptoms that should have triggered an earlier assessment.[12]

In view of the importance of understanding misdiagnosis in HF, we conducted a systematic review of the literature.

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Methods

The reporting of this systematic review is accordance to the recommendations of the PRISMA statement.[13]

Eligibility Criteria

We selected studies that evaluated the misdiagnosis of HF or cardiomyopathy. Including studies had to report one or more of the following: (i) the number of misdiagnosis of HF or cardiomyopathy cases within a defined population, (ii) factors that differ between misdiagnosed HF or cardiomyopathy, (iii) outcomes associated with misdiagnosed HF or cardiomyopathy, or (iv) reasons for misdiagnosed HF or cardiomyopathy. There was no restriction on the definition of misdiagnosis of HF or cardiomyopathy, and it was one of the aims to determine how it was defined in the literature. Outcomes included the rates of misdiagnosis and factors associated with the misdiagnosis. There was no restriction based on study design, cohort type, or language of the report, but original data had to be presented.

Search Strategy

We searched MEDLINE and EMBASE using OVID with no date or language restriction on February 15, 2021. The exact search terms were: (missed heart failure or missed cardiac failure or missed cardiomyopathy) or (missed diagnos* adj3 (heart failure or cardiac failure or cardiomyopathy)) OR (unrecogni* adj1 (heart failure or cardiac failure or cardiomyopathy)) OR (misdiagnosis and (heart failure or cardiac failure or cardiomyopathy)). These search terms are a modified version of that conducted from a previous systematic review of misdiagnosis in acute myocardial infarction.[14] We reviewed the bibliography of relevant studies and reviews for additional studies that met the inclusion criteria.

Study Selection and Data Extraction

Two reviewers (C.W.W. and C.S.K.) screened all titles and abstracts retrieved from the search for studies that met the inclusion criteria. The studies that potentially met the inclusion criteria were reviewed and the final decision to include or exclude studies was made by consensus. The data extraction was carried out by C.W.W. and C.S.K. and independently checked by J.T. Data were collected on study design, country of study origin, year, sample size, mean age, percent male, inclusion criteria, definition of missed HF or cardiac failure or cardiomyopathy, rate of missed HF or cardiac failure or cardiomyopathy, patient outcomes, initial diagnosis of misdiagnosis, and factors associated with misdiagnosis.

Risk of Bias Assessment

A methodologic quality assessment of the included studies was conducted with consideration of the following: (i) study design, (ii) reliability of ascertainment of HF, (iii) loss to follow-up or missing data, and (iv) generalizability to a general HF cohort. For the definition of HF, studies were considered high quality if they evaluated the participants against the any HF guideline criteria, confirmed with echocardiography or reviewed by a cardiologist. This process was done by 1 reviewer (C.S.K.) and checked independently by another reviewer (J.T.).

Data Analysis

Data was extracted into predesigned and piloted tables. Study findings were synthesized narratively according to whether the cohort was suspected to have HF, underlying cardiomyopathy, or was a cohort of patients with other comorbidities. Considerable heterogeneity in the study methodology meant that we did not perform statistical pooling or meta-analysis.

Results

There were a total of 10 studies after exclusion of studies that did not meet the inclusion criteria (Fig. 1).[6–11,15–18] A total of 33 studies were excluded for the following reasons: 10 were case reports, notes, letters or editorials, 7 were reviews, 2 were studies of children, 6 studies lacked data on misdiagnosis, 4 studies evaluated specific cardiomyopathies, and 4 were duplicates of included studies. The list of excluded studies is shown in Supplementary Table 1.

The study design patient characteristics and patient inclusion criteria are presented in Table 1. There were 4 prospective cohort studies, 1 retrospective cohort study, and 5 cross-sectional studies. There was a total of 223,859 patients evaluated among the studies and the mean age and percentage male were 71.9 years and 46%, respectively. The patients included among these studies varied significantly from cohorts of patients with diabetes mellitus, hypertension, COPD, shortness of breath, suspected coronary artery disease, and those in nursing homes.

The quality assessment of the included studies is shown in Table 2. There were 4 prospective studies and 9 had reliable ascertainment of HF. Loss to follow-up or missing data was classified as not reported or low in 9 studies, but only 4 studies had cohorts that were generalizable to a HF or suspected HF cohort.

Misdiagnosis in Studies of General Patients with Heart Failure

Misdiagnosis or unrecognized HF rates reported in studies of general HF patients is shown in Table 3, and the factors associated with misdiagnosis are shown in Table 4. In a study of 159 patients referred by their general practitioner for suspected HF, 68.5% did not have left ventricular dysfunction, valvular heart disease, or atrial fibrillation.[8] From emergency department settings, 14.3% of patients with a diagnosis of HF were misdiagnosed and these patients were more likely to have COPD (11.3% vs 25.9%) and less likely to have previous HF (89.6% vs 74.1%).[9] Mard et al[15] evaluated 758 patients who were discharged from the hospital

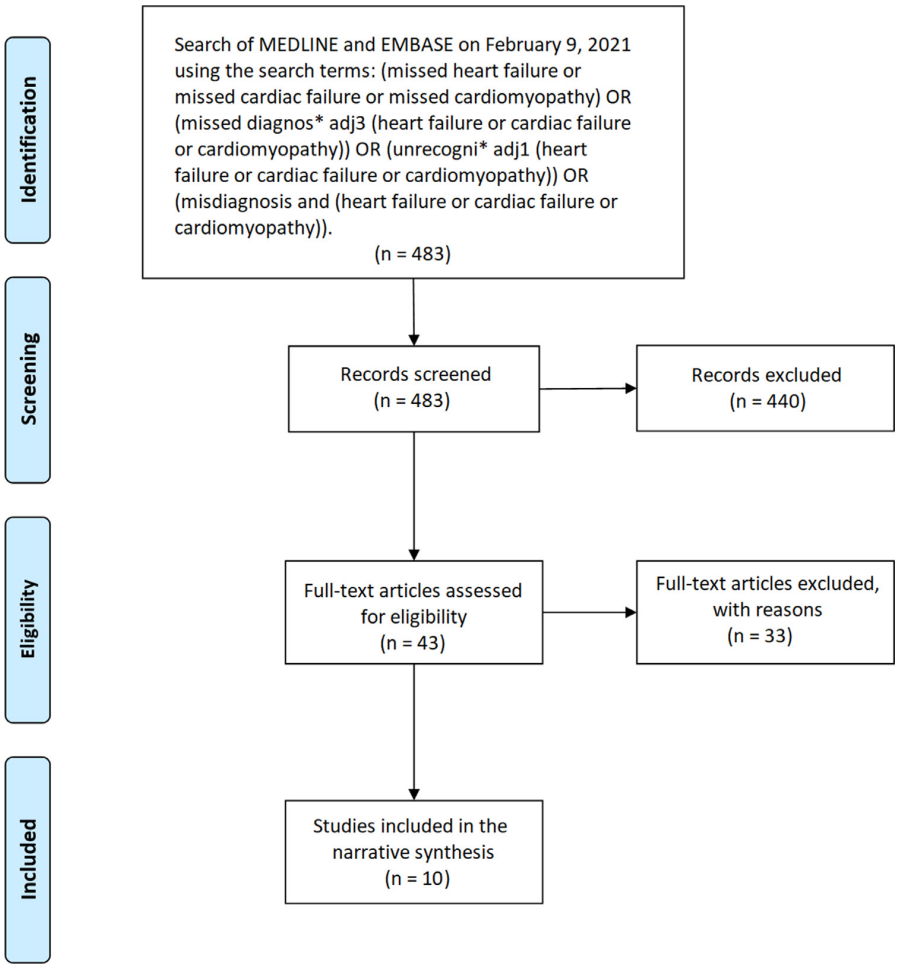

Fig. 1. Flow diagram of study inclusion.

with a diagnosis of HF and found that 16.1% did not have HF. Those with definite HF were older (75.7 years vs 69.9 years), more likely to be male (60.4% vs 43.8%), and had a history of ischemic heart disease (55.9% vs 29.8%), COPD (15.5% vs 9.9%), and atrial fibrillation (47.6% vs 19.0%).[15] Patients with definite HF also had a greater proportion with congestion on chest radiographs (43.7% vs 0%) and on medications for HF.[15] HF readmission rates among patients with definite HF were higher compared with those without HF (13.8% vs 0%).[15] Verdu-Rote et al[16] reported data from 595 patients with HF; 38.0% were misdiagnosed and factors associated with confirmed HF were ischemic heart disease (odds ratio [OR] 2.17, 95% confidence interval [CI] 1.36−3.48, $P = .01$), atrial fibrillation (OR 201, 95% CI 1.34−30.3, $P = .01$), visit by cardiologist (OR 3.66, 95% CI 2.46−5.47, $P < .01$), and use of loop diuretics (OR 3.23, 95% CI 2.14−4.89, $P < .01$).

Misdiagnosis in Other Cohorts

Table 3 and 4 show the misdiagnosis or unrecognized HF rates and predictors in specific cohorts of patients. In a population-based study of patients with type 2 diabetes mellitus, 6.8% of patients without a HF diagnosis had a mildly to severely reduced ejection fraction.[6] In a screening study of 103 nursing home residents, 14.7% were found to have a HF diagnosis that was not previously identified.[7] Barrios et al[17] studied a cohort of patients with hypertension and found that unrecognized HF was present in more than 1 in 4 patients (26.3%) and the factors most strongly associated with unrecognized HF were left ventricular hypertrophy (OR 4.84, 95% CI 4.01−5.84, $P < .0001$), cerebrovascular disease (OR 2.26 95% CI 1.87−2.73, $P < .0001$), and coronary heart disease (and no systolic blood pressure control) (OR 1.97, 95% CI 1.63−2.39, $P < .0001$). Bhatti et al[18] found that unrecognized severe left ventricular systolic dysfunction was more common in patients with anemia and chronic kidney disease (OR 2.77, 95% CI 1.53−5.0, $P = .0007$). For 405 patients with COPD, 20.5% had unrecognized HF, which included similar number for those with systolic and diastolic HF.[10] Among 585 patients older than age 65 years with shortness of breath the in Netherlands, only 16% had HF and the factors most associated with HF were older age (78.1 vs 73.3 years), a Medical Research Council score of 3 or greater

Table 1. Study Design and Patient Characteristics of Studies of Misdiagnosis in Heart Failure

Study ID	Study design; Country; Year	No. of patients	Mean age	% male	Patient inclusion criteria
Arnold et al, 2020[6]	Prospective cohort study; US; 2013−2019	215,957	70.6	47.3	Participants were diabetic patients who were prescribed with loop diuretics in the Diabetes Collaborative Registry.
Mard and Nielsen, 2010[15]	Retrospective cohort study; Denmark; 2009−2010	758	74.8	57.8	Participants were patients discharged with a diagnosis of heart failure in the Danish National Registry of Patients.
Collins et al 2006[9]	Prospective cohort study; US; 2003−2004	439	61.6	47.6	Participants were patients who presented to the emergency department with symptoms of decompensated heart failure.
Caruana et al 2000[8]	Prospective cohort study; UK; Published in 2000	159	71	31.2	Participants were patients with preserved left ventricular systolic function who were referred with suspected heart failure to an outpatient based direct access cardiography service.
Verdu-Rotellar et al 2017[16]	Cross-sectional study; Spain; 2014	595	78.3	41.9	Participants were patients aged >14 years with the diagnostic code 1.50 (congestive heart failure, left ventricular failure) according to the ICD-10.
Van Riet et al 2014[11]	Cross-sectional study; the Netherlands; 2010−2012	585	74.1	45.5	Participants were patients aged ≥65 who had presented to a GP with shortness of breath on exertion in the previous 12 months.
Barrios et al 2010[17]	Cross-sectional study; Spain; 2007	3500	73.0	0	Participants were women aged 65 years and above with an established diagnosis of arterial hypertension of ≥6 months
Bhatti et al 2009[18]	Prospective cohort study; US; published in 2009	1358	65	97	Participants were patients without history of heart failure undergoing gated myocardial perfusion SPECT for evaluation of suspected coronary artery disease.
Barents et al 2008[7]	Cross-sectional study; the Netherlands; 2004−2005	103	78	38	Participants were residents at the 'Het Zonnehuis' nursing home.
Rutten et al 2005[10]	Cross-sectional study; the Netherlands; 2001−2003	405	73.0	55.1	Participants were patients aged ≥65 with an International Classification of Primary Care code R91 (chronic bronchitis) or R95 (COPD or emphysema).

COPD, chronic obstructive pulmonary disease; ICD, *International Classification of Diseases*; GP, general practitioner; SPECT, single photon emission computed tomography.

(56.5% vs 21.3%, $P < .001$), ischemic heart disease (32.6% vs 17.4%, $P = .001$), valvular comorbidity (78.3% vs 56.6%, $P < .001$), and atrial fibrillation (18.5% vs 5.1%, $P < .001$). The use of medications—namely, loop diuretics (27.2% vs 6.1%, $P < .001$), angiotensin-converting enzyme inhibitor and angiotensin receptor blockers (64.1% vs 37.7%, $P < .001$), and beta-blockers (42.4% vs 18.1%, $P < .001$)—was more common in patients with HF and their electrocardiograms were abnormal in greater proportion (65.9% vs 32.5%, $P < .001$).[11]

Discussion

This review has several key findings. First, the misdiagnosis of patients with HF is not uncommon and the extent to which it occurs depends on the setting where the suspected diagnosis is made. Misdiagnosis ranges from 16.1% in the case of patients discharged from hospital with a diagnosis of HF to 68.5% from general practitioner referrals for HF who do not have left ventricular dysfunction, valvular heart disease, or atrial fibrillation. Second, there are certain high-risk cohorts that may have underlying HF, such as patients with ischemic heart disease, atrial fibrillation, chronic lung disease, and those receiving diuretic therapy. In these patients, a further evaluation of the symptoms and HF-specific diagnostics are likely to add value. Third, patients with suspected defined cardiomyopathies have very different rates of misdiagnosis depending on the cohort that is evaluated and the type of cardiomyopathy assessed. Finally, certain groups, such as those with COPD, stroke, and diabetes mellitus, may benefit from periodic screening for undiagnosed HF because their symptoms may masquerade as other comorbidities. These findings suggest that the misdiagnosis of HF is an important problem that should be minimized where possible to avoid delays to therapy and poor patient outcomes.

The rate of misdiagnosis or unrecognized HF is variable depending on the setting where the study took place and the population studied. From an emergency department perspective, where misdiagnosis was defined as the difference

Table 2. Quality Assessment of Included Studies

Study ID	Prospective Evaluation	Reliable Ascertainment of HF	Low Loss to Follow-up or Missing Data	Good Generalizability to a General HF Cohort
Arnold et al 2020[6]	Yes	Yes, review of charts for HF and evidence of volume overload requiring loop diuretics.	Yes, not reported.	No, diabetic patients.
Mard and Nielsen, 2010[15]	No	Yes, HF based on ESC guidelines based on symptoms and cardiac dysfunction on echocardiography.	Yes, not reported.	Yes, patients with heart failure.
Collins et al 2006[9]	Yes	Yes, HF based on symptoms and clinical judgement from the information available to clinicians.	Yes, not reported.	Yes, patients with decompensated heart failure.
Caruana et al 2000[8]	Yes	Yes, based on symptoms, signs and echocardiography.	Unclear, 50 patients not included.	Yes, patients with suspected heart failure.
Verdu-Rotellar et al 2017[16]	No	Yes, panel of specifically trained GP and a cardiologist classified HF as confirmed, unconfirmed and misdiagnosis.	Yes, not reported.	Yes, patients with heart failure.
Van Riet et al 2014[11]	No	Yes, panel of 2 cardiologist and 1 GP with specialist interest in heart failure determined HF based on test results.	Yes, not reported.	No, patients aged ≥65 years with shortness of breath on exertion.
Barrios et al 2010[17]	No	Yes, Framingham criteria for HF.	Yes, not reported.	No, women with hypertension.
Bhatti et al 2009[18]	Yes	Unclear.	Yes, not reported.	No, cohort suspected of coronary artery disease.
Barents et al 2008[7]	No	Yes, 2 experienced cardiologists independently decided on the diagnosis of HF, based on medical history, physical examination, ECG, routine blood tests and echocardiography.	Yes, 3 patients excluded for incomplete data.	No, nursing home residents.
Rutten et al 2005[10]	Yes	Yes, panel of two cardiologist, pulmonologist and GP assessed diagnostic information to confirm HF.	Yes, not reported.	No, patients with COPD.

ECG, electrocardiogram; ESC, European Society of Cardiology; HF, heart failure. Other abbreviations as in Table 1.

between the initial and final diagnosis, 14.3% of patients are misdiagnosed with HF.[9] A cross-sectional evaluation of patients with a hospital discharge diagnosis of HF found that 38.0% had normal echocardiograms.[16] Among patients with shortness of breath on exertion from a primary care perspective, only 15.7% had HF[11] and another study from primary care settings suggest that 68.5% of patients suspected to have HF do not have left ventricular dysfunction, valvular heart disease, or atrial fibrillation.[8] Even in specialist cardiac care units, 16.1% of patients with a discharge diagnosis of HF did not meet the European Society of Cardiology criteria at the time for HF.[15] In terms of unrecognized HF, the rates have been reported to be variable in cohorts of patients with chronic lung disease,[10] patients with diabetes mellitus,[6] and patients from nursing homes.[7] Recognition of the variability in reported rates of misdiagnosis or unrecognized HF is important in planning future studies. It is important to understand not only the rate at which it occurs, but also why it happens and in which populations the problem is mostly prevalent, to give insight into how it can be avoided.

Various factors are implicated in both the diagnosis and misdiagnosis of HF. Cardiovascular disease such as ischemic heart disease, atrial fibrillation, valvular heart disease, and uncontrolled systolic blood pressure have an association with undiagnosed or unrecognized HF. The association could be explained as these factors can directly contribute to cardiomyopathy or cardiac dysfunction. Noncardiovascular comorbidities such as diabetes, cognitive disorder, COPD, renal impairment, smoking, and obesity also show an association with undiagnosed or unrecognized HF. Decompensated HF may be mistaken for exacerbation of COPD, because both entities have clinical features dyspnea and similar findings on chest auscultation. Shortness of breath is a nonspecific symptom that may be attributed to obesity and peripheral edema may be falsely attributed to comorbidity-related dependent edema or adiposity in obese patients. Similarly, renal failure is known to cause fluid retention, so it is possible that there may be delay of recognition of underlying or coexisting HF. In terms of symptoms, patients who have undiagnosed HF have also been reported to present with fatigue and nocturia and may be found clinically to have an abnormal electrocardiogram.[11] One study suggests that patient who are older and female were less likely to have confirmed HF.[16] It is possible that older patients are frail and comorbid with less physical activity and the symptoms are less apparent. Equally, symptoms of HF such as fatigue and decreased functional capacity, may also be mistaken for aging, frailty, or physical deconditioning or erroneously attributed to obesity. A challenge in the interpretation of the studies is that many took place in primary care settings, where the extent of patient evaluation and testing is variable. Therefore, it is possible for patients to have factors associated with misdiagnosis, but that these issues are not captured because they have not been identified. In addition, each study considers a different combination of factors. It is important that future studies evaluating factors associated with the misdiagnosis of HF

Table 3. Study Results for Misdiagnosis or Unrecognized Heart Failure

Study ID	Setting	Definition of Misdiagnosis or Unrecognized HF	Results
Arnold et al 2020[6]	Hospital outpatient	Misdiagnosis defined no diagnosis of HF and mild to severely reduced left ventricular function.	Misdiagnosis of no HF in type 2 diabetes patients: 7129/105,148 (6.8%) had mild to severely reduced left ventricular function. Among patients with type 2 diabetes mellitus and loop diuretics, 51.3% (110,809/215,957) had a diagnosis of HF.
Mard and Nielsen, 2010[15]	Cardiac care unit	Misdiagnosis had no HF based on ESC definition.	Misdiagnosis of HF: 122/758 (16.1%).
Collins et al 2006[9]	Emergency department	Misdiagnosis defined by emergency department diagnosis of heart failure and not HF on discharge diagnosis.	Misdiagnosis of HF 63/439 (14.3%). These misdiagnosed patients more likely to have COPD ($P = .017$) and less likely to have previous HF ($P = .014$). BNP levels were lower (518 pg/mL vs 764 pg/mL, $P = .038$).
Caruana et al 2000[8]	Primary care	Misdiagnosis defined by suspected heart failure with absence of left ventricular dysfunction, valvular heart disease and atrial fibrillation.	Misdiagnosis: 109/159 (68.5%).
Verdu-Rotellar et al 2017[16]	Primary care	Typical HF signs/symptoms but no structural abnormalities on echocardiogram.	Rate of misdiagnosis: 226/595 (38.0%). Out of 226 misdiagnosed with a normal echocardiogram, 197 had symptoms/signs of HF and 29 had no symptoms/signs of HF.
Van Riet et al 2014[11]	Primary care	Unrecognized HF found on screening patients with shortness of breath on exertion and age ≥65 years.	Unrecognized HF: 92/585 (15.7%).
Barrios et al 2010[17]	Primary care	Unrecognized HF in elderly women with hypertension.	Unrecognized HF: 920/3500 (26.3%).
Bhatti et al 2009[18]	Unclear	Unrecognized HF defined by LVSD in patients with anemia and chronic kidney disease.	Unrecognized severe LVSD more common in patients with anemia and CKD (11.3% vs 4%, OR 2.77, 95% CI, 1.53−5.0, $P = .0007$).
Barents et al 2008[7]	Primary care	Unrecognized HF in nursing home residents.	Unrecognized chronic HF: 24/103 (23.3%) and 15/103 (14.6%) not detected before.
Rutten et al 2005[10]	Primary care	Unrecognized HF found in patients with stable COPD.	Unrecognized HF: 83/405 (20.5%). 42 had systolic HF and 41 had diastolic HF.

BNP, brain natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; LVSD, left ventricular systolic dysfunction; OR, odds ratio. Other abbreviations as in Tables 1 and 2.

consider a wide range of factors and also sufficient sample size to show any significant associations.

There are several reasons why patients can be misdiagnosed. First, HF shares great similarities in symptoms with chronic lung diseases where patients often present with shortness of breath on exertion and fatigue. Rutten et al[10] have investigated the prevalence of unrecognized HF in patients with stable COPD and found that 20.5% of COPD patients had unrecognized HF and, interestingly, 8.1% of the recruited COPD patients were misdiagnosed and in fact had HF. Similarly, Collin et al[9] found that patients with a previous history of COPD and without a previous history of HF were more likely to have a missed diagnosis of decompensated HF in the emergency department. Previous studies have demonstrated that chronic HF could produce a restrictive and, to a lesser degree, an obstructive picture on a pulmonary function test and be associated with gas exchange abnormalities such as a decrease in the diffusing capacity of the lungs for carbon monoxide.[19−22] It is unclear whether these changes could be associated with the high rates of misdiagnosis. In addition, the diagnosis of HF can be challenging with the subtle symptoms and signs in the case of indolent HF, in the early phases of the syndrome, and in the presence of old age and other comorbidities such as obesity.[6,10,11,15] Atrial fibrillation and myocardial ischemia have also been reported as potential causes for a HF misdiagnosis.[7,8] The lack of studies that provide information on the initial diagnosis for patients with a missed HF diagnosis is a major barriers for us to gain more insight into this area.

Although a patient exposed to misdiagnosis can come to harm from treatments that fail to alleviate symptoms, incorrect and unnecessary therapy, and disease progression, misdiagnosis has greater clinical significance if patients come to harm with misdiagnosis compared with initial correct diagnosis. Mard et al[15] was the only study to evaluate 12-month readmissions in a group of patients with a discharge diagnosis of HF. After reclassification based on reviewing the medical records for whether patients met the European Society of Cardiology criteria, they found that patients with definite HF had more readmissions for HF, acute myocardial infarction, angina pectoris, stroke, and atrial fibrillation compared with those determined to not have HF. However, those with no HF were readmitted with angina pectoris, stroke, and atrial fibrillation. More studies are needed to understand whether patients misdiagnosed have worse outcomes, particularly with respect to mortality, compared with patients with a correct initial diagnosis.

The findings of this review have several clinical implications. First, the natriuretic peptide testing and echocardiography are becoming more readily accessible and have

Table 4. Factors and Their Association With Misdiagnosis or Unrecognized HF

Study ID	Results of Factors and Association With Misdiagnosis or Unrecognized HF
Mard and Nielsen, 2010[15]	Setting: Hospital inpatients and outpatient Characteristics of patients according to definite HF vs no HF: Age: 75.7 years vs 69.9 years Male: 60.4% vs 43.8% IHD: 55.9% vs 29.8% Body mass index: 25.5 vs 28.2 Hypertension: 45.5% vs 53.7% Diabetes: 18.7% vs 16.5% Chronic obstructive pulmonary disease: 15.5% vs 9.9% Atrial fibrillation: 47.6% vs 19.0% ECG performed: 97.8% vs 91.7%• Sinus rhythm: 56.0% vs 82.0% • Atrial fibrillation: 39.2% vs 16.2% • Hypertrophy: 20.4% vs 10.8% • Ischemia: 58.4% vs 29.7% Echocardiography performed: 95.1% vs 77.7% • Left ventricular ejection fraction median: 35% vs 60% • Aortic stenosis (mild): 1.0% vs 0% • Aortic stenosis (moderate): 1.7% vs 0% • Aortic stenosis (severe): 5.3% vs 0% • Mitral valve regurgitation (mild): 36.8% vs 15.4% • Mitral valve regurgitation (moderate): 15.2% vs 0% • Mitral valve regurgitation (severe): 4.2% vs 0% • Tricuspid regurgitation (40 mm Hg) 20.4% vs 0% Chest radiographs performed: 79.7% vs 62.8% • Pulmonary congestion: 43.7% vs 0%
Collins et al 2006[9]	Settings: Emergency department Evaluation of nonprimary vs primary HF: Age: 58.5 vs 66.7, $P < .001$ History of CHF: 74.1% vs 89.6%, $P = .014$ History of COPD: 25.9% vs 11.3%, $P = .017$ Mean BNP: 518 vs 764, $P = .038$
Verdu-Rotellar et al 2017[16]	Setting: Primary care Increased odds of confirmed diagnosis: IHD: OR 2.17, 95% CI 1.36–3.48, $P = .01$ Atrial fibrillation: OR 2.01, 95% CI 1.34–30.3, $P = .01$ Visits by cardiologist: OR 3.66, 95% CI 2.46–5.47, $P < .01$ Reduced odds of confirmed diagnosis: Age (per year): OR 0.97, 95% CI 0.95–0.99, $P = .04$ Women: OR 0.74, 95% CI 0.49–1.13, $P = .16$
Van Riet et al 2014[11]	Setting: Primary care Characteristics of elderly patients with newly detected HF vs no HF: Age (mean): 78.1 vs 73.3 years, $P < .001$ MRC score 3: 56.5% vs 21.3%, $P < .001$ Nocturia twice or more per night: 33.7% vs 22.3%, $P = .02$ Fatigue: 53.3% vs 38.9%, $P = .01$ IHD: 32.6% vs 17.4%, $P = .001$ Valvular comorbidity: 78.3%, 56.6%, $P < .001$ Hypertension: 72.8% vs 49.3%, $P < .001$ Diabetes: 22.8% vs 11.8%, $P = .004$ Previous stroke or TIA: 16.3% vs 7.3%, $P = .005$ Hypercholesterolemia: 40.2% vs 30.4%, $P = .06$ Atrial fibrillation: 18.5% vs 5.1%, $P < .001$ Noncardiovascular comorbidities: Cognitive disorders: 27.2% vs 17.2%, $P = .03$ Body mass index (mean): 29.9 vs 27.2, $P < .001$ Rales: 28.3% vs 16.8%, $P = .01$ Peripheral edema: 48.9% vs 20.5%, $P < .001$ NT-proBNP (median, IQR): 46 (24–89) vs 13 (7–20), $P < .001$ Abnormal ECG: 65.9% vs 32.5%, $P < .001$
Barrios et al 2010[17]	Setting: Primary care Predictive factors involved in unrecognized HF: Left ventricular hypertrophy: OR 4.84, 95% CI 4.01–5.84, $P < .0001$ Cerebrovascular disease: OR 2.26, 95% CI 1.87–2.73, $P < .0001$ Coronary heart disease: OR 1.98, 95% CI 1.56–2.51, $P < .0001$ No systolic blood pressure control: OR 1.97, 95% CI 1.63–2.39, $P < .0001$ Microalbuminuria: OR 1.61, 95% CI 1.26–2.06, $P = .0002$ Renal impairment: OR 1.58, 95% CI 1.26–1.97, $P < .0001$ Smoking: OR 1.49, 95% CI 1.12–1.98, $P = .0066$ Obesity: OR 1.31, 95% CI 1.10–1.57, $P = .0032$

CHF, congestive heart failure; IHD, ischemic heart disease; IQR, interquartile range; MRC, Medical Research Council; NT-proBNP, N-terminal pro-brain natriuretic peptide; TIA, transient ischemic attack. Other abbreviations as in Tables 1–3.

shown to be reliable HF screening tests.[23] This practice has revolutionized the screening and diagnosis of HF, because most primary care physician have access. Second, the shift should be on education about HF, recognizing that HF could be undetected in high-risk cohorts and patients could present with early or atypical symptoms. Last, it might be worth considering screening patients with COPD for HF; Rutten et al[10] have demonstrated the high prevalence of undetected HF (19.6%) and HF misdiagnosis (8%) in this cohort. HF therapies, composed of disease-modifying medications and device-based therapies, have been shown to improve survival. In view of these considerations, an early and accurate diagnosis, coupled with timely intervention, may prevent irreversible damage or poor outcomes that are associated with HF with reduced ejection fraction.

The findings of the systematic review may be subject to bias and methodologic heterogeneity of the included studies. In particular, there was no consistent definition for misdiagnosis, but this factor may actually reflect real-world practices, where there are major differences between initial diagnoses made in primary care settings and emergency departments, which see different populations and have access to different levels of investigations. However, the summary of the literature presented in this review has value because its information can help to plan future studies that build and improve on what is known.

There are several limitations in this review. A limitation of this review is that 1 study accounted for 97% of the total patients in the analysis. This study used 2 mechanisms to study misdiagnosis, the first considering patients without a HF diagnosis but with some degree of reduced left ventricular function, and a second method of considering the proportion of patients on loop diuretics who had a HF diagnosis. This type of data may not be reliable compared with other the smaller studies where diagnoses were ascertained on clinical evaluation and tests. However, it does illustrate how it is possible to study misdiagnosis in certain large cohorts. In addition, there are few contemporary studies and we included studies that were published up to 20 years ago before natriuretic peptide testing became commonplace; as a result, a significant number of studies did not measure the natriuretic peptides.[8,10,15] Furthermore, the assessment of diastolic function was not performed routinely at the beginning of the millennia. The study conducted by Verdu-Rotellar et al[16] was undertaken more recently, but natriuretic peptide testing was not available in their primary care setting at the time. In addition, some of the older studies did not use guidelines to help guide HF diagnosis.[8,9]

In conclusion, the misdiagnosis of HF occurs in everyday clinical practice and it can range from 16% to 69%, depending on the study population. Clinical suspicion of HF should be heightened in patients with ischemic heart disease, atrial fibrillation, chronic lung disease, diabetes mellitus, stroke, and those receiving diuretic therapy in whom the likelihood of a confirmed HF diagnosis is increased. Natriuretic peptide and echocardiographic assessments are easily performed in addition to clinical evaluation. More studies in contemporary settings and practices are needed to understand how often misdiagnosis occurs as well as the patient outcomes associated with a misdiagnosis of HF.

Conflicts of interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2021.05.014.

References

1. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail 2020;8:1342–56.
2. Bragazzi NL, Zhong W, Shu J, Much AA, Lotan D, Grupper A, et al. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. Eur J Prev Cardiol, in press. 2021. https://doi.org/10.1093/eurjpc/zwaa147. doi.org/.
3. Jones NR, Roalfe AK, Adoki I, Hobbs R, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail 2019;11:1306–25.
4. Centers for Disease Control and Prevention. Heart failure. Available at: https://www.cdc.gov/heartdisease/heart_failure.htm#:~:text=Facts%20About%20Heart%20Failure%20in, estimated%20%2430.7%20billion%20in%202012. Last accessed 4 Mar 2021.
5. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics −2020 update: a report from the American Heart Association. Circulation 2020;141:e139–596.
6. Arnold SV, Jones PG, Beasley M, Cordova J, Goyal A, Fonarow GC, et al. Heart failure documentation in outpatients with diabetes and volume overload: an observational cohort study from the Diabetes Collaborative Registry. Cardiovasc Diabetiol 2020;19:212.
7. Barents M, van der Horst ICC, Voors AA, Hillege JL, Muskiet FAJ, de Jongste MJL. Prevalence and misdiagnosis of chronic heart failure in nursing home residents: the role of B-type natriuretic peptides. Neth Heart J 2008;16:123–8.
8. Caruana L, Petrie MC, Davie AP, McMurray JJV. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. BMJ 2000;321:215–8.
9. Collins SP, Lindsell CJ, Peacock WF, Eckert DC, Askew J, Storrow AB. Clinical characteristics of emergency department heart failure patients initially diagnosed as non-heart failure. BMC Emerg Med 2006;6:11.
10. Ruttens FH, Cramer MM, Grobbee DE, Sachs APE, Kirkels JH, Lammers JJ, et al. Unrecognized heart failure in elderly patients with stable chronic pulmonary disease. Eur Heart J 2005;18:1887–94.
11. Van Riet EES, Hoes AW, Limburg A, Landman MAJ, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. Eur Heart J 2014;16:772–7.
12. Bottle A, Kim D, Aylin P, Cowie M, Majeed A, Hayhoe B. Routes to diagnosis of heart failure: observational study using linked data in England. Heart 2018;104:600–5.

13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
14. Kwok CS, Bennett S, Azam Z, Welsh V, Potluri R, Loke YK, et al. Misdiagnosis of acute myocardial infarction: a systematic review of the literature. Crit Pathw Cardiol, in press 2021. https://doi.org/10.1097/HPC.0000000000000256.
15. 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;2:235–9.
16. Verdu-Rotellar JM, Frigola-Capell E, Alvarez-Perez R, da Silva D, Enjuanes C, Domingo M, et al. Validation of heart failure diagnosis registered in primary care records in two primary care centres in Barcelona (Spain) and factors related. A cross-sectional study. Eur J Gen Pract 2017;23:107–13.
17. Barrios V, Escobar C, Sierra ADL, Llisterri JL, Gonzalez-Segura D. Detection Of Unrecognized Clinical Heart Failure in elderly hypertensive women attended in primary care setting. Blood Press 2010;19:301–7.
18. Bhatti S, Hakeem A, Cook JK, Dillie KS, Chang SM. Unrecognized severe left ventricular dysfunction in patients with anemia and chronic kidney disease and future risk of death and heart failure hospitalization. JACC 2009;53:A183.
19. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJV. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail 2009;11:130–9.
20. Olson TP, Kenneth CB, Johnson BD. Pulmonary function changes associated with cardiomegaly in chronic heart failure. J Card Fail 2007;13:100–7.
21. Dimopoulou I, Daganou M, Tsintzas OK, Tzelepis GE. Effect of severity of longstanding congestive heart failure on pulmonary function. Respir Med 1998;92:1321–5.
22. Light RW, George RB. Serial pulmonary function in patients with acute heart failure. Arch Intern Med 1983;143:429–33.
23. Hildebrandt P, Collinson PO, Doughty RN, Fuat A, Gaze DC, Gustafsson F, et al. Age-dependent values of N-terminal pro-B-type-natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care. Eur Heart J 2010;31:1881–9.