**Misdiagnosis of heart failure: A systematic review of the literature**

**Short title:** Misdiagnosis of heart failure

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**Highlights**

* Misdiagnosis of heart failure (HF) ranges from 16% to 68% depending on the setting.
* Patients with ischemic heart disease and lung disease are at risk of HF misdiagnosis.
* Patients with lung disease, stroke and diabetes may benefit from screening for HF.

**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 due to similar symptoms with other conditions especially respiratory diseases.

**Methods:** 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.

**Results:** 10 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 19.6% of patients and 8% had misdiagnosis of HF as COPD. Another study suggests that anemia and chronic kidney disease is associated with an increase in 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 misdiagnosis of HF.

**Conclusion:** Misdiagnosis of HF is an unfortunate part of everyday clinical practice which occurs with 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.

**Keywords:** Heart failure; diagnosis; misdiagnosis; systematic review

**Introduction**

Heart failure (HF) is a global problem responsible for considerable morbidity and mortality.[[1]](#endnote-1) There are an estimated 64.34 million patients[[2]](#endnote-2) with HF globally, with the 5-year mortality as high as 43.3%.[[3]](#endnote-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]](#endnote-4),[[5]](#endnote-5) While 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]](#endnote-6)

HF is a clinical syndrome characterized by dyspnea, orthopnea, peripheral oedema 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,[[7]](#endnote-7),[[8]](#endnote-8),[[9]](#endnote-9),[[10]](#endnote-10),[[11]](#endnote-11) These comorbidities cause dyspnea and reduced exercise tolerance which are often the main symptoms of HF. In addition, the early recognition of HF in the ambulatory setting is challenging as the disease is often progresses slowly with only subtler signs or symptoms leading to delay or initial missed diagnosis.6 Registry data indicates that 80% of HF diagnoses are made in hospital, despite 40% of patients having symptoms that should have triggered an earlier assessment.[[12]](#endnote-12)

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

**Methods**

The reporting of this systematic review is accordance to the recommendations of the PRISMA Statement.[[13]](#endnote-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 in 15 February 2020. 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]](#endnote-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 (CWW and CSK) 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 CWW and CSK and independently checked by JT. Data was collected on study design, country of study origin, year, sample size, mean age, % 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*

Methodological 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, 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 was done by one reviewer (CSK) and checked independently by another reviewer (JT).

*Data analysis*

Data was extracted into pre-designed and piloted tables. Study findings were narratively synthesized 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 (Figure 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 studies 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, chronic obstructive pulmonary disease, 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 cohort that were generalizable to a HF or suspected HF cohort.

*Misdiagnosis in studies of general heart failure patients*

Misdiagnosis or unrecognized HF rates reported in studies of general HF patients is shown in Table 3 while the factors associated with misdiagnosis is shown in Table 4. In a study of 159 patients referred by their GP 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 evaluated 758 patients who were discharged from hospital with a diagnosis of HF and found that 16.1% did not have HF.[[15]](#endnote-15) Those with definite HF were older (75.7 vs 69.9 years), 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 Definite HF patients also had greater proportion with congestion on chest X-ray (43.7% vs 0%) and on medications for HF.15 HF readmission rates among patients with definite HF was higher compared to those without HF (13.8% vs 0%).15 Verdu-Rote et al reported data from 595 patients with HF; 38.0% were misdiagnosed and factors associated with confirmed HF were ischemic heart disease (OR 2.17 95%CI 1.36-3.48, p=0.01), atrial fibrillation (OR 201 95%CI 1.34-30.3, p=0.01), visit by cardiologist (OR 3.66 95%CI 2.46-5.47, p<0.01) and use of loop diuretics (OR 3.23 95%CI 2.14-4.89, p<0.01).[[16]](#endnote-16)

*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 type 2 diabetes mellitus patients, 6.8% of patients without a HF diagnosis had mild 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 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<0.0001), cerebrovascular disease (OR 2.26 95% CI 1.87-2.73, p<0.0001), coronary heart disease (and no systolic blood pressure control (OR 1.97 95%CI 1.63-2.39, p<0.0001).[[17]](#endnote-17) Bhatti et al 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=0.0007).[[18]](#endnote-18) For 405 patients with chronic obstructive pulmonary disease, 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 in Netherlands, only 16% had HF and the factors most associated with HF were older age (78.1 vs 73.3 years), MRC score ≥3 (56.5% vs 21.3%, p<0.001), ischemic heart disease (32.6% vs 17.4%, p=0.001), valvular comorbidity (78.3% vs 56.6%, p<0.001) and atrial fibrillation (18.5% vs 5.1%, p<0.001). Use of medications loop diuretics (27.2% vs 6.1% p<0.001), ACEi/ARB (64.1% vs 37.7%, p<0.001) and beta-blockers (42.4% vs 18.1%, p<0.001) was more common in patients with HF and their ECG were abnormal in greater proportion (65.9% vs 32.5%, p<0.001).11

**Discussion**

This review has several key findings. First, misdiagnosis of HF patients 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 diagnosis of HF to 68.5% from GP referrals for HF who do not have left ventricular dysfunction, valvular heart disease or atrial fibrillation. Secondly, there are certain high-risk cohort which may have underlying HF such as patients with ischemic heart disease, atrial fibrillation, chronic lung disease and those receiving diuretic therapy. In these patients, further evaluation of symptoms and HF specific diagnostics are likely to add additional value. Third, patients with suspected defined cardiomyopathies have very different rates of misdiagnosis depending on the cohort which 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 as symptoms may masquerade as other co-morbidities. These findings suggest that misdiagnosis of HF is an important problem which 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 population. From an emergency department perspective where misdiagnosis was defined as difference between 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 16% had HF11 and another study from primary care settings suggest that 69% 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, 16.0% of patients with a discharge diagnosis of HF did not meet the ESC criteria at the time for HF.15 In terms of unrecognized HF, the rates have been reported to be variable in cohorts of chronic lung disease,10 diabetes mellitus6 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. Non-cardiovascular comorbidities such as diabetes, cognitive disorder, COPD, renal impairment, smoking and obesity also show association with undiagnosed or unrecognized HF. Decompensated HF may be mistaken for exacerbation of COPD as both have clinical features dyspnea and similar findings on chest auscultation. Shortness of breath is a non-specific symptom which may be attributed to obesity and peripheral oedema may be falsely attributed to comorbidity related dependent oedema 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 co-existing 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 abnormal ECG.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 so symptoms are less apparent. Equally symptoms of HF such as fatigue and reduced 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 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 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 misdiagnosis 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 has investigated the prevalence of unrecognized HF in patients with stable COPD which found that 19.6% of COPD patients had unrecognized HF and interestingly, 8% of the recruited COPD patients were misdiagnosed and in fact had HF.10 Similarly, Collin et al found that patient with a previous history of COPD and without previous history of HF were more likely to have an ED missed diagnosis of decompensated HF.9 Previous studies have demonstrated that chronic HF could produce restrictive and to a lesser degree obstructive picture in pulmonary function test and associated with gas exchange abnormalities such as reduction in the diffusing capacity of the lungs for carbon monoxide.[[19]](#endnote-19),[[20]](#endnote-20),[[21]](#endnote-21),[[22]](#endnote-22) It is unclear if 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 indolent HF, in the early phases of the syndrome and in the presence of old age and other co-morbidities such as obesity.6,10,11,15 Atrial fibrillation and myocardial ischemia have also been reported as potential causes for HF misdiagnosis.7,8 The lack of studies that provide information on the initial diagnosis for patients with missed HF diagnosis is a major barriers for us to gain more insight into this area.

While 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 to initial correct diagnosis. Mard et al 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 ESC criteria, they found that patients with definite HF had greater readmissions for HF, acute myocardial infarction, angina pectoris, stroke and atrial fibrillation compared to those determined to not have HF. However, those with no HF were readmitted with angina pectoris, stroke and atrial fibrillation. More studies are needed in order to understand whether patients misdiagnosed have worse outcomes, particularly in respect to mortality, compared to patients with correct initial diagnosis.

The findings of this review have several clinical implications. Firstly, the natriuretic peptide testing and echocardiography are becoming more readily accessible and have shown to be reliable HF screening tests.[[23]](#endnote-23) This has revolutionized screening and diagnosis of HF as most primary care physician have access. Secondly, the shift should be on education about HF, recognizing HF could be undetected in high-risk cohorts and patients could present with early or atypical symptoms. Lastly, it might be worth to consider screening COPD patients for HF as Rutten et has demonstrated the high prevalence of undetected HF (19.6%) and HF misdiagnosis (8%) in such cohort.10 HF therapies, comprised of disease modifying medications and device based therapies have been shown to improve survival. In view of these considerations 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 methodological heterogeneity of the included studies. In particular there was no consistent definition for misdiagnosis but this 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 as its information can help plan future studies which build and improve on what is known.

There are several limitations in this review. A limitation of this review is that one study accounted for 97% of the total patients in the analysis. This study used two mechanisms to study misdiagnosis; the first considering patients without a HF diagnosis but with degree of reduce 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 to 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 the natriuretic peptide testing became commonplace and as a result a significant number of studies did not measure the natriuretic peptides.8,10,15 Furthermore, assessment of diastolic function was not routinely performed at the beginning of the millennia. The study conducted by Verdu-Rotellar et al was done more recently but the natriuretic peptide testing was not available in their primary care setting at the time.16 In addition, some of the older studies did not use guidelines to help guide HF diagnosis.8,9

In conclusion, 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 therapying whom likelihood of a confirmed HF diagnosis is increased. Natriuretic peptide and echocardiographic assessment are easily performed in addition to clinical evaluation. More studies in contemporary settings and practices are needed to understand how often misdiagnosis occurs and patient outcomes associated with misdiagnosis of HF.

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**Figure 1: Flow diagram of study inclusion**

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**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 20206 | 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 201015 | 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 20069 | 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 20008 | 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 201716 | Cross-sectional study; Spain; 2014. | 595 | 78.3 | 41.9 | Participants were patients aged above 14 years with the diagnostic code 1.50 (congestive heart failure, left ventricular failure) according to the ICD-10. |
| Van Riet 201411 | Cross-sectional study; Netherlands; 2010-2012. | 585 | 74.1 | 45.5 | Participants were patients aged 65 and above who had presented to a GP with shortness of breath on exertion in the previous 12 months. |
| Barrios 201017 | Cross-sectional study; Spain; 2007. | 3,500 | 73.0 | 0 | Participants were women aged 65 years and above with an established diagnosis of arterial hypertension of at least 6 months. |
| Bhatti 200918 | Prospective cohort study; US; published in 2009 | 1,358 | 65 | 97 | Participants were patients without history of heart failure undergoing gated myocardial perfusion SPECT for evaluation of suspected coronary artery disease. |
| Barents 20087 | Cross-sectional study; Netherlands; 2004-2005. | 103 | 78 | 38 | Participants were residents at the ‘Het Zonnehuis’ nursing home. |
| Rutten 200510 | Cross-sectional study; Netherlands; 2001-2003. | 405 | 73.0 | 55.1 | Participants were patients aged 65 and above with an International Classification of Primary Care code R91 (chronic bronchitis) or R95 (COPD or emphysema). |

**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 20206 | Yes | Yes, review of charts for HF and evidence of volume overload requiring loop diuretics. | Yes, not reported. | No, diabetic patients. |
| Mard 201015 | No | Yes, HF based on ESC guidelines based on symptoms and cardiac dysfunction on echocardiography. | Yes, not reported. | Yes, patients with heart failure. |
| Collins 20069 | 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 20008 | Yes | Yes, based on symptoms, signs and echocardiography. | Unclear, 50 patients not included. | Yes, patients with suspected heart failure. |
| Verdu-Rotellar 201716 | 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 201411 | No | Yes, panel of two cardiologist and one GP with specialist interest in heart failure determined HF based on test results. | Yes, not reported. | No, patients aged 65 years or greater with shortness of breath on exertion. |
| Barrios 201017 | No | Yes, Framingham criteria for HF. | Yes, not reported. | No, women with hypertension. |
| Bhatti 200918 | Yes | Unclear. | Yes, not reported. | No, cohort suspected of coronary artery disease. |
| Barents 20087 | 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 200510 | Yes | Yes, panel of two cardiologist, pulmonologist and GP assessed diagnostic information to confirm HF. | Yes, not reported. | No, patients with COPD. |

**Table 3: Study results for misdiagnosis or unrecognized heart failure**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study ID** | **Setting** | **Definition of misdiagnosis/unrecognized HF** | **Results** |
| Arnold 20206 | 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: 7,129/105,148 (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 201015 | Cardiac care unit | Misdiagnosis had no HF based on ESC definition. | Misdiagnosis of HF: 122/758 (16.1%). |
| Collins 20069 | Emergency department | Misdiagnosis defined by ED 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=0.017) and less likely to have previous HF (p=0.014). BNP levels were lower (518 pg/ml vs 764 pg/ml, p=0.038). |
| Caruana 20008 | 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 201716 | Primary care | Typical HF signs/symptoms but no structural abnormalities on echocardiogram. | Rate of misdiagnosis: 226/595 (38.0%). Out of 226 misdiagnosed with normal echo, 197 had symptoms/signs of HF and 29 had no symptoms/signs of HF. |
| Van Riet 201411 | 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 201017 | Primary care | Unrecognized HF in elderly women with hypertension. | Unrecognized HF: 920/3500 (26.3%). |
| Bhatti 200918 | 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=0.0007. |
| Barents 20087 | Primary care | Unrecognized HF in nursing home residents. | Unrecognized chronic HF: 24/103 (23.3%) and 15/103 (14.6%) not detected before. |
| Rutten 200510 | Primary care | Unrecognized HF found in patients with stable chronic obstructive pulmonary disease. | Unrecognized HF: 83/405 (20.5%). 42 had systolic HF and 41 had diastolic HF. |

HF=heart failure; ESC=European Society of Cardiology; LVSD=left ventricular systolic dysfunction; CKD=chronic kidney disease; BNP=brain natriuretic peptide.

**Table 4: Factors and their association with misdiagnosis or unrecognized heart failure**

|  |  |
| --- | --- |
| **Study ID** | **Results of factors and association with misdiagnosis or unrecognized HF** |
| Mard 201015 | Setting: Hospital inpatients and outpatient  Characteristics of patients according to definite HF vs no HF:  Age: 75.7 vs 69.9 years  Male: 60.4% vs 43.8%  Ischemic heart disease: 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% * Ischaemia 58.4% vs 29.7%   Echo 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 (40mmHg and above) 20.4% vs 0%   Chest X-ray performed: 79.7% vs 62.8%   * Pulmonary congestion 43.7% vs 0% |
| Collins 20069 | Settings: Emergency department  Evaluation of non-primary vs primary HF:  Age: 58.5 vs 66.7, p<0.001  History of CHF: 74.1% vs 89.6%, p=0.014  History of COPD: 25.9% vs 11.3%, p=0.017  Mean BNP: 518 vs 764, p=0.038 |
| Verdu-Rotellar 201716 | Setting: Primary care  Increased odds of confirmed diagnosis:  Ischemic heart disease: OR 2.17 95%CI 1.36-3.48, p=0.01  Atrial fibrillation: OR 2.01 95%CI 1.34-30.3, p=0.01  Visits by cardiologist: OR 3.66 95%CI 2.46-5.47, p<0.01  Reduced odds of confirmed diagnosis:  Age (per year): OR 0.97 95%CI 0.95-0.99, p=0.04  Women: OR 0.74 95%CI 0.49-1.13, p=0.16 |
| Van Riet 201411 | Setting: Primary care  Characteristics of elderly patients with newly detected HF vs no HF:  Age (mean): 78.1 vs 73.3 years, p<0.001  MRC score ≥3: 56.5% vs 21.3%, p<0.001  Nocturia twice or more per night: 33.7% vs 22.3%, p=0.02  Fatigue: 53.3% vs 38.9%, p=0.01  IHD: 32.6% vs 17.4%, p=0.001  Valvular comorbidity: 78.3%, 56.6%, p<0.001  Hypertension: 72.8% vs 49.3%, p<0.001  Diabetes: 22.8% vs 11.8%, p=0.004  Previous stroke or TIA: 16.3% vs 7.3%, p=0.005  Hypercholesterolaemia: 40.2% vs 30.4%, p=0.06  Atrial fibrillation: 18.5% vs 5.1%, p<0.001  Non-cardiovascular comorbidities:  Cognitive disorders: 27.2% vs 17.2%, p=0.03  Body mass index (mean): 29.9 vs 27.2, p<0.001  Rales: 28.3% vs 16.8%, p=0.01  Peripheral oedema: 48.9% vs 20.5%, p<0.001  NTproBNP (median, IQR): 46 (24-89) vs 13 (7-20), p<0.001  Abnormal ECG: 65.9% vs 32.5%, p<0.001 |
| Barrios 201017 | Setting: Primary care  Predictive factors involved in unrecognized HF:  Left ventricular hypertrophy: OR 4.84 95%CI 4.01-5.84, p<0.0001  Cerebrovascular disease: OR 2.26 95%CI 1.87-2.73, p<0.0001  Coronary heart disease: OR 1.98 95%CI 1.56-2.51, p<0.0001  No systolic blood pressure control: OR 1.97 95%CI 1.63-2.39, p<0.0001  Microalbuminuria: OR 1.61 95%CI 1.26-2.06, p=0.0002  Renal impairment: OR 1.58 95%CI 1.26-1.97, p<0.0001  Smoking: OR 1.49 95%CI 1.12-1.98, p=0.0066  Obesity: OR 1.31 95%CI 1.10-1.57, p=0.0032 |

**Supplementary Table 1: Excluded studies and reasons for exclusion**

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| --- | --- | --- | --- |
| **Authors** | **Title** | **Journal** | **Reason for exclusion** |
| Suwanwongse K., Shabarek N. | Cough syncope in a patient with asthma exacerbation leads to the new diagnosis of heart failure. | Chest. Conference: CHEST 2020 Annual Meeting. 158 (4 Supplement) (pp A2298), 2020. | Exclude, case report |
| Liu Y., Wu Q. | The clinical and echocardiographic analysis of noncompaction cardiomyopathy in misdiagnosis and missed diagnosis. | Russian Journal of Cardiology. 111 (7) (pp 34-41), 2014. | Exclude, cardiomyopathy |
| Homar V., Mirosevic S., Svab I., Lainscak M. | Natriuretic peptides for heart failure screening in nursing homes: a systematic review. | Heart Failure Reviews. (no pagination), 2020. | Exclude, review |
| Jurko T., Mistinova M., Jurko A., Minarik M., Mestanik M., Tonhajzerova I. | Risk of misdiagnosis in children with left ventricular non-compaction-potential benefit of magnetic resonance imaging. | European Heart Journal Cardiovascular Imaging. Conference: 22nd Annual Meeting of the European Association of Echocardiography, EUROECHO 2018. Italy. 20 (Supplement 1) (pp i800), 2019. | Exclude, cardiomyopathy |
| Dungu J.N. | Cardiac amyloid - An update. | European Cardiology Review. 10 (2) (pp 113-117), 2015. | Exclude, review |
| Falcao de Campos C., Parreira S., Conceicao I. | Misdiagnosis in late versus early onset hATTR amyloidosis patients: experience from a reference centre. | Amyloid. 26 (sup1) (pp 37-38), 2019. | Exclude, letter |
| Puri K., Singh H., Denfield S.W., Cabrera A.G., Dreyer W.J., Tunuguntla H.P., Price J.F. | Missed Diagnosis of New-Onset Systolic Heart Failure at First Presentation in Children with No Known Heart Disease. | Journal of Pediatrics. 208 (pp 258-264.e3), 2019. | Exclude, children |
| He S., Tian Z., Guan H., Li J., Fang Q., Zhang S. | Clinical characteristics and prognosis of Chinese patients with hereditary transthyretin amyloid cardiomyopathy. | Orphanet Journal of Rare Diseases. 14 (1) (no pagination), 2019. Article Number: 251. | Exclude, not misdiagnosis |
| Guder G., Stork S. | COPD and heart failure: differential diagnosis and comorbidity. | Herz. 44 (6) (pp 502-508), 2019. | Exclude, review |
| Fatima A., Maron M., Maron B., Rowin E. | Identification of cardiac amyloidosis among a cohort of hypertrophic cardiomyopathy patients. | Journal of the American College of Cardiology. Conference: 68th Annual Scientific Session of the American College of Cardiology: ACC.19. United States. 73 (9 Supplement 1) (pp 1009), 2019. | Exclude, cardiomyopathy |
| Gonzalez P.J., Bossolo A.G., Mangual M.M., Torres K., Martinez J.H. | An unrecognized heart failure in elderly; the myxedema heart. | Endocrine Reviews. Conference: 99th Annual Meeting of the Endocrine Society, ENDO 2017. United States. 38 (3 Supplement 1) (no pagination), 2017. | Exclude, case report |
| Skinner T.R., Scott I.A., Martin J.H. | Diagnostic errors in older patients: A systematic review of incidence and potential causes in seven prevalent diseases. | International Journal of General Medicine. 9 (pp 137-146), 2016. | Exclude, review |
| Kimani K., Grant L., Murray S. | Experiences and expectations of patients living with advanced heart failure in Kenya. | Palliative Medicine. Conference: 11th Palliative Care Congress. United Kingdom. 30 (4) (pp S9), 2016. | Exclude, no data |
| van Riet E., Hoes A., Limburg A., Landman M., van der Hoeven H., Rutten F. | Unrecognized heart failure in elderly patients with shortness of breath. | Huisarts en Wetenschap. 58 (7) (pp 354-357), 2015. | Duplicate |
| Van Riet E.E.S., Rutten F.H., Limburg A., Landman M.J., Hoes A.W. | High prevalence of unrecognized heart failure among elderly patients presenting with shortness of breath on exertion to the general practitioner. | European Journal of Heart Failure. Conference: Heart Failure Congress 2013. Lisbon Portugal. Conference Publication: (var.pagings). 12 (SUPPL. 1) (pp S182), 2013. | Duplicate |
| Van Mourik Y., Bertens L.C.M., Reitsma J.B., Moons K.G.M., Hoes A.W., Rutten F.H. | Community-dwelling frail elderly with shortness of breath: Unrecognized heart failure and/or COPD or other diseases?. | European Journal of Heart Failure, Supplement. Conference: Heart Failure 2012. Belgrade Serbia. Conference Publication: (var.pagings). 11 (SUPPL. 1) (pp S13), 2012. | Exclude, no data |
| Bae B.J., Kim H.J., Kim S.J., Lee K.Y., Kim W.D., Yoo K.H. | A case of yellow nail syndrome: Misdiagnosis as congestive heart failure. | Tuberculosis and Respiratory Diseases. 71 (1) (pp 46-49), 2011. | Exclude, case report |
| Boonman-de Winter L.J., Rutten F.H., Cramer M.J., Liem A.H., Landman M.J., van Stel H.F., de Wit G.A., Rutten G.E., van Hessen P.A., Hoes A.W. | Early recognition of heart failure in patients with diabetes type 2 in primary care. A prospective diagnostic efficiency study. (UHFO-DM2). | BMC public health. 9 (pp 479), 2009. | Exclude, no data |
| Hawkins N.M., Petrie M.C., Jhund P.S., Chalmers G.W., Dunn F.G., McMurray J.J.V. | Heart failure and chronic obstructive pulmonary disease: Diagnostic pitfalls and epidemiology. | European Journal of Heart Failure. 11 (2) (pp 130-139), 2009. | Exclude, review |
| Nair S.B., Khattar R.S. | Isolated left ventricular non-compaction: An emerging cause of heart failure in adults. | Postgraduate Medical Journal. 85 (1002) (pp 202-207), 2009. | Exclude, review |
| Duygu H., Zoghi M., Nalbantgil S., Ozerkan F., Akilli A., Akin M., Onder R., Erturk U. | Apical hypertrophic cardiomyopathy might lead to misdiagnosis of ischaemic heart disease. | International Journal of Cardiovascular Imaging. 24 (7) (pp 675-681), 2008. | Exclude, cardiomyopathy |
| Jolobe O.M. | Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease | European Heart Journal. 27 (3) (pp 372), 2006. Date of Publication: February 2006. | Exclude, letter |
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