Low-output heart failure: A review of clinical status and meta-analysis of diagnosis and clinical management methods

Aref Albakri*

Department of Internal Medicine, St-Marien hospital Bonn Venusberg, Bonn, Germany

Abstract

Low-output heart failure (LoHF) is an uncommon form of heart failure (HF) but one that signals very advanced HF. It is associated with ominous prognosis as well as substantial morbidity and mortality. However, LoHF remains largely under-researched. The traditional description of HF focused on congestive heart failure (CHF) marked by low cardiac output and accompanied by pulmonary/peripheral congestion. This focus contributed to under-appreciation of LoHF patients who have little or no evidence of congestion. Moreover, LoHF patients have no proven therapy and the selection of appropriate treatment depends on individual pathophysiology and underlying aetiology. LoHF patients have heterogeneous aetiology and pathophysiology highlighting the importance of in-depth understanding of its clinical features, diagnosis and clinical management, which forms the basis of the present review.

Introduction

Despite remarkable advancements in medical and surgical therapies, effective management of heart failure (HF) continues to pose significant challenges to healthcare providers. The challenge is reflected by high rates of HF-related hospital readmissions along with increased mortality and morbidity [1]. Part of the challenge is very heterogeneous aetiology, pathophysiology, and clinical presentations of different forms of HF, in which some HF forms have a paucity of clinical trial data and consequently a limited understanding. In particular, the traditional description of HF has been almost synonymous with congestive heart failure (CHF) yet the term CHF excludes a minority of HF patients who have little or no demonstrable symptoms of pulmonary and/or peripheral congestion [2]. Low-output HF (LoHF) has also been linked with an ominous prognosis and signals very advanced HF. Moreover, symptomatic and pathophysiological differences in CHF and LoHF support the need for different clinical management approaches [3]. Despite these differences, traditional HF therapies have been generalized to all forms of HF including CHF and LoHF, creating a clinical need to understand the pathophysiology, diagnosis and clinical management of LoHF. In this article, we aggregate published evidence on LoHF in terms of epidemiology, aetiology, pathophysiology, diagnosis and clinical management. The intention is to revamp the knowledge of the clinical status of LoHF as well as improve clinical management of HF in general.

Definition

Heart failure is a complex clinical syndrome marked by structural and/or functional myocardial defects leading to impaired ventricular filling or ejection [4,5]. The complexity of the syndrome is evident in its heterogeneous classifications: right-, left- or bi-ventricular based on defect location; acute or chronic based on time of onset; preserved, borderline or reduced ejection fraction based on functional status; low-or high-output based on cardiac output (CO), and forward or backward failure based on the direction of blood flow. Each of these classifications is significant for the diagnosis and treatment of HF [4,5]. Despite the several classifications, the term CHF has traditionally been used interchangeably with HF but which does not sufficiently describe LoHF because of several symptomatic and pathophysiological differences.

LoHF, also known as low CO in acute decompensated HF, describes a high-acuity form of HF characterized by decreased forward CO (cardiac index [CI] < 2.0 L/min/m² and systolic blood pressure [BP] < 90 mmHg) and end-organ hypoperfusion with little or no evidence of pulmonary congestion [6]. LoHF is distinct from CHF, which describes HF characterized by reduced CO causing to pulmonary and peripheral congestion leading to dyspnoea and peripheral oedema respectively [7]. The 2005 European Society of Cardiology (ESC) guidelines on diagnosis and management of HF [8] suggest a continuum from low cardiac output syndrome (LCOS) to LoHF to cardiogenic shock. The ESC guidelines define cardiogenic shock as evidence of tissue perfusion induced by HF after the correction of pre-load characterized by systolic BP < 90 mmHg or a drop of mean arterial pressure > 30 mmHg; urine output < 0.5 ml/kg/h; pulse rate > 60 beats per minute (bpm) with or without evidence of congestion [8]. LCOS on the other hand is common in post-operative HF patients and defined as the need for post-operative intra-aortic balloon pump or inotropic support for greater than 30 minutes in an acute care setting [6].

Epidemiology

The exact prevalence and incidence of LoHF in the general population is completely unknown. At present, there are no population-based epidemiological data specific to LoHF. The only available data are from single-centre clinical trials investigating a select population of HF patients who have undergone cardiac surgery. In 1975, Parr et al. [9] made the seminal description of the clinical entity of LCOS and reported an incidence of 25% in children who had undergone cardiac surgery based on decreased CO defined as CI < 2.0 L/min/m². Two decades later, Wernovsky et al. [10] demonstrated the same incidence of post-operative LCOS in patients who had undergone arterial switch operation occurring within 6-18 hours post-surgery. Much recent clinical trials report a wide variation in prevalence, from 3.6% (men) and 5.9% (women) [11] to 9.1% [12] and to 41% [13] and an incidence of 14.7% [14]. In a recent long-term (twenty-year: 1990-2009) prospective clinical trial involving 25,176 consecutive coronary artery by-pass graft (CABG) surgery patients, Algarni et al. reported the prevalence of post-operative LCOS decreased significantly from 9.1% (1990-1994) to 2.4% (2005-2009) [15].

Aetiology

The aetiology of LoHF is multi-factorial. Generally, it is a consequence of left ventricle (LV), right ventricle (RV) or systemic ventricle (single ventricle anatomy) dysfunction and can include either or both systolic and/or diastolic dysfunction [16]. Perturbations in ventricular filling or ejecting lead to LoHF, which is a frequent complication in patients who have undergone cardiac surgery or are in cardiogenic shock [6]. It may present as an acute deterioration in patients with chronic HF or it may be transient and reversible episode with resolution of the acute trigger. It is a clinical syndrome considered the final pathway of a multitude of diseases affecting cardiac function. It is not sufficient to make diagnosis of LoHF, the underlying cause or trigger must also be determined, and if possible, treated [16,17]. Table 1 provides a summary of conditions causing low-output state in HF patients.

Pathophysiology

The current understanding of the pathophysiology of LoHF largely relies on the evidence from clinical trials on post-operative CABG patients [9-12]. The pathologic hallmark is excessively depressed CO accompanied by end-organ hypoperfusion. Physiologically, the heart functions as a pump to distribute oxygenated blood in sufficient quantities to satisfy metabolic needs of tissues. Since metabolic needs vary under normal and stressful situations, CO also varies to satisfy this dynamic demand [18]. The diastolic phase of the cardiac cycle is critical in LoHF patients because it is during ventricular relaxation that coronary filling occurs to provide myocardial oxygenation [19]. Heart rate (HR) is also significant in diastole because too rapid HR prevents the heart from achieving complete myocardial relaxation and perfusion. Thus, cardiac dysfunction results from structural (residual cardiac anomaly) or functional cardiac disorder (disturbances in ventricular filling or emptying, or increased systemic vascular resistance [SVR]).

Pathophysiologically, CO is dependent on the HR and the stroke volume (SV) (CO = HR * SV). Stroke volume in turn is the net product of three inter-related circulation variables: preload, afterload and contractility. If one or more of these components is impaired, a low-cardiac output state can develop [6]. Moreover, these components affect both systolic and diastolic phases of the cardiac cycle causing LV/RV systolic dysfunction and/or diastolic dysfunction also known as HF with preserved ejection fraction (Figure 1). Other conditions such as valvular heart disease, pulmonary hypertension (PH), mechanical valve dysfunction, and respiratory failure can precipitate or aggravate the development of LoHF [17].
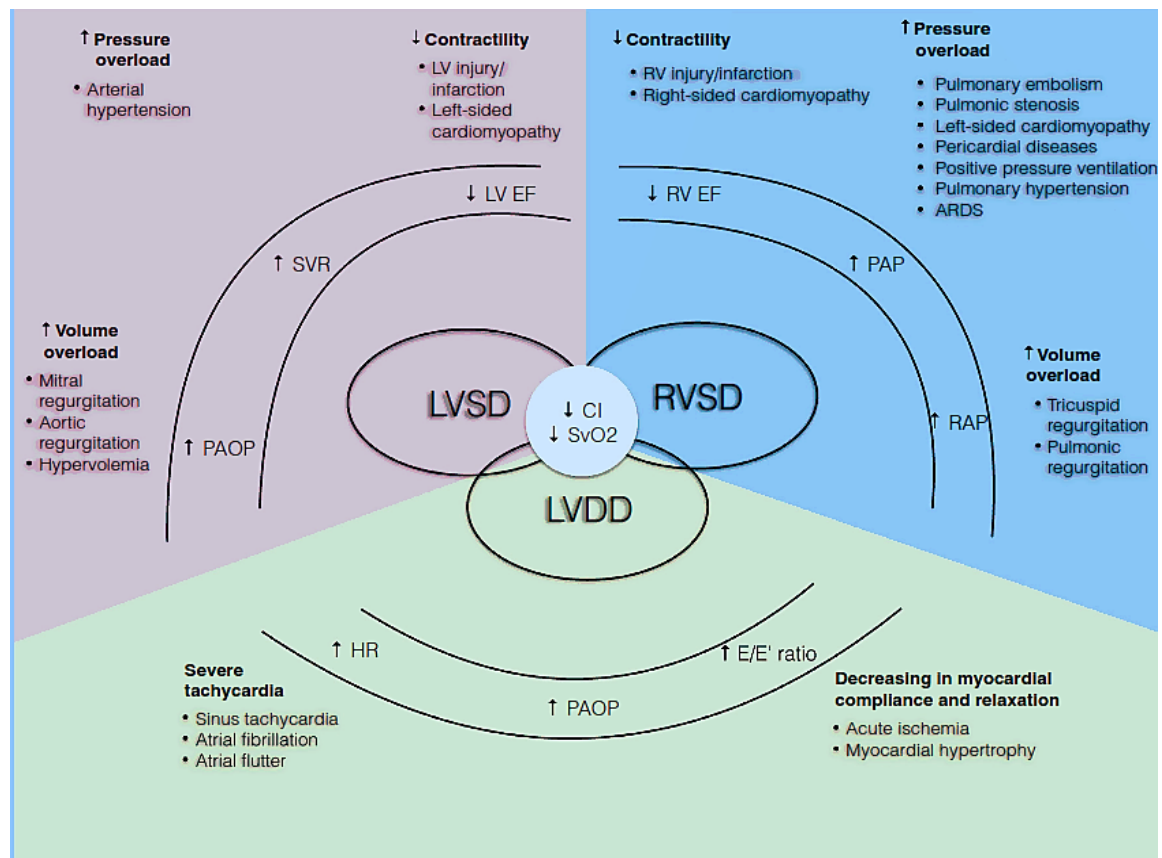
LV ystolic dysfunction

Left ventricular (LV) systolic dysfunction (or depressed LV ejection fraction [LVEF]) is the most common pathophysiologic mechanism seen in LoHF patients. Circulation variables affecting LV systolic function are preload, after load, and contractility [17]. Generally, LV systolic dysfunction is a consequence of the loss or reduction of functional cardiomyocytes resulting from necrosis due to impaired coronary circulation and ischemia, reperfusion injury or the less understood natural phenomenon of cardiomyocyte apoptosis [20-22]. The loss of functional cardiomyocytes can be transient as seen during myocardial stunning defined as a viable myocardium salvaged by coronary reperfusion, which exhibits prolonged post-ischemic dysfunction following reperfusion [23]. The loss of functional cardiomyocyte can also be refractory to reversal in conditions such as infection; tachycardia; valvular disease; metabolic disorders such as acidosis, hypoglycemia, hypocalcaemia; exposure to environmental cardiac toxins and chemicals; idiopathic dilated cardiomyopathy (DCM); and genetic disorders such as familial DCM, hypertrophic cardiomyopathy and muscular dystrophies [17]. Impaired cardiac response to preload causes a dramatic decrease in CO and oxygen delivery to other key body organs, elevated atrial pressure, capillary wedge pressure, and cardiogenic pulmonary oedema. Although compensatory changes in the LV adapts to relatively high systemic arterial pressure, significant increase in afterload can induce LV systolic dysfunction [17].

LV diastolic dysfunction

Although uncommon, LoHF can develop in patients with LV diastolic dysfunction with preserved LVEF. The condition results from the inability of the ventricular chamber to fill with adequate volume of blood despite normal preload, which presents as diastolic dysfunction [24]. Underlying conditions such as severe tachycardia, decreased myocardial compliance, or abnormal ventricular relaxation impairs the relaxation and filling of the LV during the diastole phase of cardiac cycle. At the cardiomyocyte level, these conditions are associated with calcium removal from the cytosol and calcium homeostasis, the adequacy of cross-bridge detachment and intrinsic functional

Table 1. Aetiology of low-output state by pathophysiology

Mechanisms	Causative Conditions
Loss of myocardial contractility	Coronary artery disease, cardiomyopathy, myocarditis, decompensated chronic HF, post-cardiac surgery, toxins, nutrition (obesity)m infiltrative diseases, end stage renal failure, Chagas disease or HIV infection
Impaired ventricular filling or ejecting	Pericarditis, pericardial effusion, cardiac tamponade, tension pneumothorax, pulmonary embolism, valvular disease, hypertension, volume overload, cardiomyopathy (hypertrophic/restrictive)
Abnormal Signalling	Tachyarrhythmia, bradyarrhythmia,
Non-cardiovascular factors	Infection, sepsis, major surgery, asthma, severe brain injury
High output states	Thyrotoxicosis (hyperthyroidism), sepsis, anaemia, arteriovenous shunting

Figure 1. Pathophysiologic mechanisms of low-output heart failure

Common causes and typical; symptoms of LoHF are included. The major pathophysiological mechanisms of LoHF is ventricular dysfunction: LV systolic and/or diastolic dysfunction and RV systolic dysfunction, all of which share common pathologic features of reduced cardiac index (CI) and reduced mixed venous oxygen saturation (SvO$_2$). LV and RV systolic dysfunction results from increased pressure overload, increased volume overload and decreased contractility while LV diastolic dysfunction results from severe tachycardia and decreased myocardial compliance and relaxation. Adapted from Lomivorotov et al. 2017, p. 293 [17]

cytoskeletal element disorder [25]. Cross-bridge detachment can contribute to delayed isovolumic relaxation time, which results in decreased LV stroke volume especially at higher HR [26]. LV relaxation also depends on sarcoplasmic reticular calcium ion re-uptake and nitric oxide signalling, which also facilitate cross-bridge detachment. Since the process of cross-bridge detachment is energy consuming, it can cause a deficit in myocardial energy and consequently slow down LV myocardial relaxation [27,28].

Despite diastolic dysfunction being a widespread phenomenon seen in up to 70% of post-operative cardiac patients [29,30], diastolic dysfunction alone is insufficient to explain the development of acute HF. In the setting of other clinical conditions such as atrial fibrillation (AF), impaired coronary circulation, and arterial hypertension, diastolic dysfunction can result in decompensated state, and thus believed to be an early sign of myocardial ischemia [17]. The dynamic relationship between the LV diastolic and systolic functions also contributes to diastolic dysfunction in LoHF patients. Stimulation of inotropic catecholamine affects both diastole and systole, and can enhance diastolic dysfunction. Depressed LVEF leads to an increase in end-systolic volume and prolongs the diastolic phase of the cardiac cycle [17].

RV dysfunction

In LoHF, particularly after coronary artery surgery, the principle pathophysiologic mechanisms of RV dysfunction include increased preload, increased afterload, impaired right coronary artery perfusion and decreased contractility [31-33]. In contrast to left coronary artery, the perfusion of the right coronary artery occurs during both diastole and systole. The presence of PH causes an increase in RV pressure leading to decreased right coronary artery perfusion, which explains the importance for providing optimal left and right coronary circulation [17]. In patients who have undergone coronary artery surgery, RV dysfunction can develop as the result of a combination of mechanisms. Perioperative RV ischemia and infarction are the major causes of impaired RV contractility. Tricuspid or pulmonic regurgitation re common causes of increased volume preload while left-sided valvular disease or cardiomyopathy, PH or pulmonary embolism (PE), acute respiratory distress syndrome and high positive pressure ventilation are common causes of pressure overload [34]. Since the RV normally allows low-pressure perfusion of the pulmonary vasculature, it is highly sensitive even to moderate increases in pulmonary artery pressure (PAP). RV failure can develop in the setting of PH or impaired contractility associated with a rapid progression of RV dilation leading to increased end-diastolic RV pressure [35]. These physiologic alterations can cause inter-ventricular septum shift towards an already under-filled LV chamber and consequently cause a reduction in LV preload and a decrease in CO [36].

Risk Factors

Risk factors for LoHF remains an under-researched area. However, little data available from clinical trials on HF [37] and from post-

operative LCOS patients [9-12, 38-39] provide valuable insights into risk factors and predictors of LoHF. In analysis of 452 patients hospitalized with decompensated HF and low cardiac output, significant risk factors for LoHF were Chagas disease (Relative risk [RR]: 3.66), depressed ejection fraction (RR: 2.41), hyponatremia (RR: 1.62) and renal dysfunction (RR: 1.92) [37]. Risk factors for post-operative LoHF include impaired LV function (< 50%), on-pump CABG, emergency or cardiopulmonary bypass (CPB) surgery, incomplete revascularization, age > 65 years, and a combined presence of diabetes mellitus and pre-operative renal dysfunction [9-12. Malnutrition is another important risk factor associated with increased the likelihood of post-operative inotropic support and independently predicts adverse post-operative clinical outcomes [40]. In addition to patient and operation risk factors, biochemical predictors of LoHF in post-operative patients are low haemoglobin levels [41], total lymphocyte count < 2000 cells/μL [42], and pre-operative levels of serum natriuretic peptides [43,44]. Over the past two decades, there have been changes in the trends in some recognised risk factors. Factors such as hypertension, female sex, triple vessel disease and left main disease are no longer statistically significant while the risk associated with depressed pre-operative ejection fraction has doubled [15].

Diagnosis

There is no consensus guidelines or proven diagnostic criteria for LoHF patients. In addition, clinical signs and symptoms are non-specific. In the absence of standardized guidelines, diagnosis usually relies on accepted collection of hemodynamic and physiologic aberrations useful for raising clinical suspicion of LoHF [16]. Diagnosis of LoHF alone is often not enough. The cause of the low-output state also has to be established. In some causes of low-output state such as PE or MI, treating the underlying cause is the most important consideration and thus it is imperative to make the diagnosis. Since LoHF patients are often unstable, it is also common for clinical evaluation, diagnosis and treatment to occur concurrently more so in acute care settings [4].

Signs and symptoms

Low cardiac output as the presenting feature of acute decompensated HF is uncommon, affecting only 8.9 to 9.6% of hospitalized HF patients [45,46]. LoHF may share many clinical features with CHF but there are notable differences that may support or guide subsequent diagnostic decisions. Excessive fatigue and increased exercise intolerance are important initial signs noticed by LoHF patients even prior to diagnosis [4,5]. In addition, LoHF patients commonly present with agitation, confusion and/or reduced levels of consciousness; cold/vasoconstricted peripheries or delayed capillary refill time; hypotension; tachycardia or bradycardia; thready pulse; raised jugular venous pressure; breathlessness and hypoxaemia; and oliguria/anuria [3,4]. These signs and symptoms can differ between low perfusion and congestion in HF patients (Table 2).

Initial clinical evaluation

History and physical examination: The 2016 ESC guidelines on diagnosis and management of HF emphasize on the importance of obtaining detailed patient history and physical examination on all patients suspected to have HF [4]. Detailed history from the patient, or relative and friends if the patient is too unwell, should focus on obtaining information about symptoms, previous and current cardiac and extra-cardiac conditions capable of precipitating or aggravating HF, exposure to risk factors of HF or of low-output state, and medication history for previous and current medical conditions [4]. In addition

to patient history, physical examination is recommended to all LoHF patients to assess for clinical indicators for hemodynamic, peripheral perfusion, congestion, underlying aetiology and valvular pathology. Hemodynamic parameters of interest include blood pressure, HR and heart rhythm, gallop rhythm, oxygen saturation, and respiratory rate [47]. Tests for peripheral perfusion should include consciousness levels, peripheral skin/central temperature, capillary refill time, and urine output. Tests for congestion include raised jugular venous pressure, peripheral/pulmonary oedema, hepatomegaly, ascites and pleural effusions. Tests for the underlying aetiology should incorporate cardiovascular examination, and heart sound and murmurs. Finally, evidence for valvular dysfunction should include pericardial rub and evidence of pericardial effusion with or without cardiac tamponade [48].

The combination of patient history and physical examination have proven invaluable in the assessment of hemodynamic status and recognition of LoHF [49]. In 1976, Forrester et al. [50] conducted physical examination of patients with acute myocardial infarction and identified four hemodynamic profiles (A, B, L and C) as illustrated in Figure 2. Hemodynamic profiles are based on presence or absence of pulmonary congestion (pulmonary capillary wedge pressure [PCWP] > or ≤ 18 mmHg) and the adequacy of perfusion (CI > 2.2 L/min/m²). Profile A represents no congestion/hypoperfusion; Profile B congestion without hypoperfusion; Profile C hypoperfusion without congestion;

Table 2. Symptoms and signs of low perfusion vs. congestion in heart failure patients

Low Perfusion	Congestion
Fatigue	Fatigue
Confusion	Tachycardia
Agitation	Raised jugular venous pressure
Low level of consciousness	Breathlessness and hypoxemia
Cold peripheries	Pulmonary oedema
Delayed capillary refill time	Lowe extremities oedema
Thready pulse	Hepatic congestion
Hypotension	
Tachycardia	
Oliguria or anuria	
Metabolic acidosis	
SvO$_2$ < 65%	
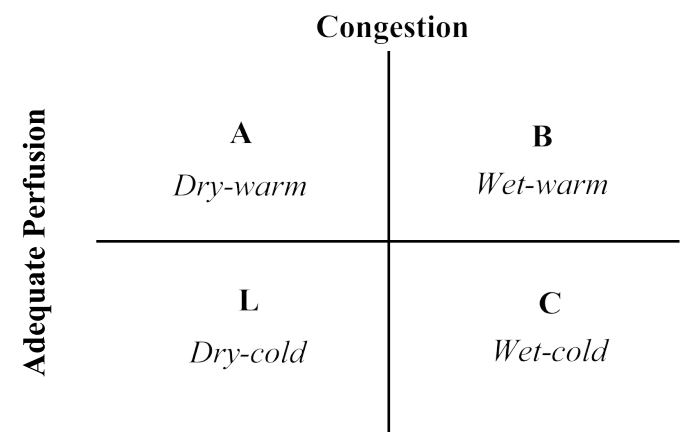
Figure 2. Schematic presentation of clinical profile of acute decompensated heart failure

Congestion is assessed by the presence of orthopnoea, jugular venous distension, pulmonary rales, hepatojugular reflux, ascites, peripheral oedema, abdominal reflux and Valsalva square wave. Low perfusion was assessed by the presence of a narrow pulse pressure, pulsus alterations, cold extremities, maybe sleepy, declining serum sodium levels and worsening renal function. Adapted from Nohria, **et al.** [47]

and Profile L congestion and hypoperfusion [51]. LoHF patients fall under Profiles L and C (hypoperfusion ± congestion based on Nohria et al. [49] demonstration that Profile L and C have an average CI of 1.6 L/min/m^2 and 1.9 L/min/m^2 respectively.

Electrocardiogram (ECG): Both AHA [4] and ESC [5] guidelines on HF recommend that electrocardiogram (ECG) should be performed as early as possible in all patients suspected with HF. ECG can demonstrate a variety of abnormalities and is very unlikely to be normal in HF patients. It may also provide evidence of an underlying aetiology of cardiac dysfunction including bradycardia, atrioventricular block, sinus tachycardia, atrial or ventricular tachyarrhythmia, ischemia, LV hypertrophy and low voltage complexes [5].

Basic laboratory tests: The AHA and ESC HF guidelines [4,5] also recommend basic laboratory tests in the initial clinical evaluation to support diagnosis of HF or of the cause of the low-output state. Blood tests should be performed in all suspected HF patients. Haemoglobin (Hb > 10 g/dL) indicates optimal oxygen delivery to tissues), chronic anaemia is common in chronic HF and markedly increased white blood cells raise the suspicion for alternative diagnosis. Tests for serum electrolyte to determine levels of potassium, magnesium and calcium. Urea and creatinine tests to assess renal hypoperfusion and dysfunction common in HF. Tests for impaired liver function, which suggest impaired RV and/or hepatic congestion. Glucose test to assess for hypoglycaemia that can impair cardiac function. Thyroid function tests for hypo- or hyper-thyroidism that can cause intrinsic myocardial infarction. Finally, tests for serum natriuretic peptides whose elevated levels indicate increased ventricular wall stress but which does not detect abrupt changes in ventricular filling pressures because of their long half-life [3-5].

Cardiac imaging tests: Cardiac imaging plays a central role in the diagnosis of HF as well as in monitoring and guiding therapy. Echocardiography is the preferred modality for reasons of accuracy, availability, safety and cost-effectiveness [52-54]. It may be complemented by other imaging modalities selected based on the ability to answer specific clinical questions while considering contraindications and risks [55,56].

Echocardiography: Echocardiography is strongly recommended for all suspected patients because of its ability to confirm or exclude clinical diagnosis of LoHF, to assess SV and its variations, and to determine the cause of low-output state [47,54,55]. Transthoracic echocardiography should be performed as soon as possible following clinical diagnosis of low-cardiac output. Not only does it measure the extent of systolic and diastolic dysfunction, it also provides valuable information about ventricular morphology, valvular dysfunction, myocardial and pericardial disease and regional wall motion abnormalities [5]. Echocardiography evaluates systolic function by measuring LEVF, where > 45-50% is considered normal. On the other hand, diastolic function is evaluated using mitral in flow patterns, pulmonary vein flow and tissue Doppler at the mitral annulus, while CO and SV are evaluated using the Doppler principle. Pulmonary artery pressure (PAP) can be estimated by measuring regurgitate jet velocity. High PAP in the presence of dilated RV with septal flattening or bowing into the LV indicating acute increase in RV pressure raising clinical suspicion of PE as the cause of low output state [47,54,56].

Chest X-ray: Chest x-ray could be considered in patients suspected with LoHF. Important indicators that should considered for assessment include enlarged heart indicating cardiomegaly or LV hypertrophy; pulmonary venous congestion indicating elevated LV filling pressure; and pleural effusion indicating elevated LV pressure, pulmonary embolism or post-cardiac surgery([45].

Coronary angiography: Indications for coronary angiography in LoHF patients should be in concordance with the recommendation of relevant consensus guidelines for HF [3-5]. In HF patients presenting with chest pain and evidence of ST-elevation myocardial infarction (STEMI) on ECG, revascularization using primary percutaneous coronary intervention should be performed as soon as possible. Coronary angiography should also be considered in patients with post-cardiac arrest of ischemic aetiology, when there is evidence of HF and in patients who have recovered from low-output state when the cause has not been determined [5].

Clinical management

The presence of LoHF represents a very high-risk condition requiring prompt treatment but lacks standardized guidelines for clinical management [16]. Consequently, clinicians normally consider individual pathophysiology to select the most appropriate treatment strategy [57]. In acute LoHF patients, the 2016 ESC HF guidelines recommend the use of hemodynamic profiles (based on the presence or absence of congestion and adequacy of perfusion) to guide clinical management [5]. For LoHF patients in Profile L (no congestion but hypoperfused) and Profile C (both congestion and hypoperfused) who are in acute decompensation state, emergency treatment goals can include resuscitating patients, restoring oxygenation, improving organ perfusion and optimizing hemodynamic (stroke volume and CO), and resolving symptoms. Other subsequent goals include optimal monitoring and establishing the underlying cause of low cardiac output and treating the cause if reversible [50,51,57]. At present, available therapeutic targets for LoHF are optimizing tissue oxygenation, stabilizing circulation and treating reversible causes of low-output state (Figure 3).

Optimize tissue oxygenation (ventilatory strategies)

Clinical management of LoHF patients often begins with the assessment of airway, breathing and circulation for evidence of peripheral hypoperfusion. Ventilator strategies such as oropharyngeal or nasopharyngeal airways are common adjuncts used to restore or maintain airway patency in LoHF patients with decreased levels of consciousness due to decreased cerebral perfusion. Additional endotracheal intubation should be considered if the patient remains with compromised airways [58]. If patients continues to remain hypoxic (SaO$_2$ < 95%), maximization of oxygen delivery using high flow oxygen, continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV) can be considered. In patients with no improvement, intubation or ventilation can be considered [59].

Stabilize circulation

Cardiac output (CO) is a function of HR and SV. In turn, SV depends on four circulation variables – heart rate, preload, contractility and afterload. Optimizing all these variables will improve CO in LoHF patients [49,51]. In clinical setting, strategies to increase CO depend on the underlying cause and the affected circulation variable [16]. Clinical interventions include volume adjustment, pharmacological support and device therapy.

Heart Rate/Rhythm: As part of the body's physiological response, increasing HR increases CO. Too fast or slow HR has a detrimental effect on CO. In LoHF patients with tachycardia (too fast resting HR > 100 bpm) who are distressed, restless and dyspnoeic, morphine may
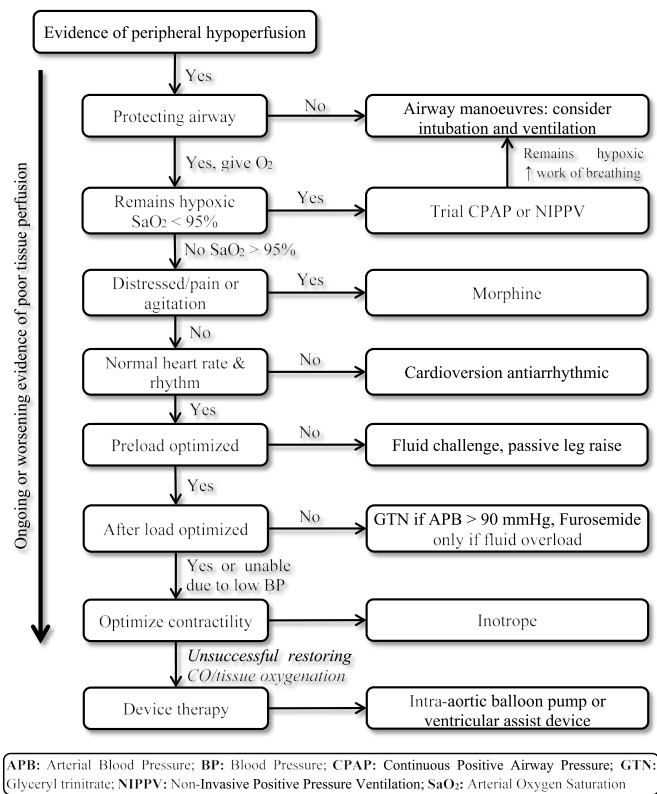
Figure 3. Treatment algorithm for low-output heart failure

Treatment of LoHF targets improving tissue oxygenation and stabilizing circulation based on ongoing or worsening symptom of tissue perfusion. Treatment begins by improving ventilation using delivery of high flow oxygen, continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV). If unsuccessful, cardioversion or antiarrhythmic drugs are given to normalize heart rate, fluid challenge to optimize pre-load, and/or vasodilators and inotropes to manipulate and improve contractility respectively. If previous ventilation and medication are unsuccessful in restoring cardiac output and/or tissue oxygenation, device therapy using intra-aortic balloon pump or ventricular assist devices can be considered

be administered to relieve dyspnoea, pain and agitation as well as it is a mild venodilator for reducing afterload especially in CPAP or NIPPV patients [58]. If HR < 40 bpm with evidence of hemodynamic compromise and/or impaired CO, medication that increase HR (atropine and anticholinergics [Glycopyrrolate]) or interventions such as transcutaneous/transvenous pacing should be performed. Urgent electrical cardioversion should be considered in selected LoHF with ventricular/supraventricular tachycardia or rapid AF with evidence of cardiovascular compromise [4,5].

Optimize preload (Volume adjustments): Measurement of preload is essential for its optimization. It is recommended in patients with clinical evidence of impaired peripheral perfusion. A fluid challenge should be performed to assess preload responsiveness. Rapidly infusing 250 ml fluid (crystalloid or colloid) for over five minutes and objectively assessing the effect on SV. If the effect is an increase or decrease > 10%, the patient should continue receiving fluid boluses to optimise preload until they are no longer fluid responsive [16]. For patients with signs of congestion and pulmonary oedema who do not require fluid bolus, a passive leg raise can be done – lifting the patient's leg to 45 degrees to exclude the need for fluid challenge. If the response if favourable a real fluid challenge can be given [16].

Manipulate afterload (Pharmacological support): Afterload is the resistance against which the ventricle is ejecting blood, at times estimated as SVR. Afterload should be reduced in LoHF patients presenting with a high afterload, low CO, evidence of poor peripheral perfusion and pulmonary oedema. Pharmacological support using vasodilators should be given to LoHF patients with systolic BP ≥110 mmHg. In patients with systolic BP < 90 mmHG and mean arterial pressure < 65 mmHg, vasodilators are not recommended because of the risk of hypotension, which can complicate organ perfusion. In these patients, inotropes is recommended as the first line of treatment [51].

Improve contractility (Pharmacological support): If the patient persist with evidence of tissue hypoperfusion or reduced oxygen delivery despite interventions for heart rate, preload and afterload, treatment to improve contractility should be considered. Meanwhile, optimizing oxygen delivery should be continued to aim for haemoglobin ≥10 g/dl and ensuring optimal oxygen saturations (SaO_2). Factors adversely affecting myocardial contractility are hyperkalaemia, hypomagnesemia, hypocalcaemia, severe acidosis, hypoxia and hypoglycemia, which must be corrected. Inotropes are recommended to improve contractility and subsequently CO in LoHF patients with low BP and/or low CI in the presence of signs of poor peripheral perfusion or congestion [49,51]. However, pharmacological support using Dobutamine (an inotrope) should be used with caution in patients who have tachycardia or AF because it increases AV node conduction and can precipitate fast ventricular rhythms [5]. On the other hand, levosimendan is recommended in LoHF patients with acute myocardial ischemic or post cardiac surgery since it does not increase myocardial oxygen demand [5]. Long-term effect of inotropes could be detrimental and thus their use should be stopped once stability has been achieved. Vasopressors should not be the first-line medication in low-output states as they increase SVR and subsequently impair CO. However, a dual therapy of vasopressors and inotrope is recommended in patients having sepsis as the underlying cause of low-output state [51].

Device therapy: Device therapy should be considered in LoHF patients when optimal medical therapies have been unsuccessful in restoring CO and tissue oxygenation. Common device therapies include intra-aortic balloon pump (IABP) and ventricular assist device (VAD). The use of IABP is common in LoHF patients with ischemic heart disease, pre or post-percutaneous intervention or post-cardiac surgery. IABP comprises of a balloon inserted into the aorta through the femoral artery. The balloon inflates during diastole and deflates during systole to increase diastolic BP and consequently coronary perfusion, and reduces afterload thereby increasing CO [60]. On the other hand, the use of VAD is uncommon. It can only be used in specialist centres. It is commonly used as a bridge to cardiac transplantation in patients with favourable quality of life or to recovery in patients with acute myocarditis [61].

Treating underlying causes

Some causes of low-output state in patients with LoHF can be reversed with specific therapies. Reversible causes should be identified early during initial clinical evaluation. These causes include acute myocardial infarction, cardiac tamponade, tension pneumothorax, pulmonary embolism, and acute valve failure [16,17]. (Table 3).

Meta-analysis of diagnosis and clinical management

The basis of clinical diagnosis of LoHF has been echocardiographic evidence of LV/RV systolic dysfunction and/or LV diastolic dysfunction accompanied by evidence of reduced CO and SvO2 [5]. Hemodynamic

Table 3. Therapies for causes of low-output stated in low-output heart failure

Underlying Disease	Recommended Therapies
Acute myocardial infarction	Re-establish coronary circulation: primary percutaneous coronary intervention if unavailable thrombolysis. Antiplatelet therapy for patients with ST-segment elevation myocardial infarction.
Cardiac tamponade	Percutaneous or surgical draining of pericardial effusion causing hemodynamic compromise
Tension pneumothorax	Insert large cannula into the 2nd intercostal space in the mid-clavicular line on the affected side to let air out and then insert a chest drain
Pulmonary embolism	Thrombolysis, thrombectomy/embolectomy
Acute valve failure	Referral to the cardiothoracic surgeon

profiles based on measures of congestion and perfusion have been used to classify acute HF patients into four profiles: dry-warm (A), wet-warm (B), dry-cold (L) and wet-cold (C) and useful in identifying LoHF patients [51,53]. LoHF patients have been classified into Profiles (L) and (C) based on the presence/absence of congestion and/or the inadequacy of peripheral perfusion [53]. These two hemodynamic profiles have formed the basis for selecting patients with LoHF in clinical trials as well as provide simple bedside assessment to help classify patients at the time of presentation and to guide the selection of initial therapies [51,62]. The goal of the present meta-analysis is to aggregate published evidence of common diagnostic features and treatment outcomes for patients with LoHF.

Search strategy

Three major online databases (PubMed, EMBASE and Cochrane) were systematically searched since inception to December 2018 for studies investigating diagnosis and clinical management of LoHF. To avoid overlooking studies that did not mention LoHF in the title or abstract, the first 200 relevance-ranked articles retrieved with a full-text Google Scholar search were included. No publication time or language restrictions were applied. Additional studies were identified through a manual search of the list of references from the included studies as well as from relevant review articles, which were then subjected to the inclusion criteria. The search criteria included population of interest (patients with LoHF or LCOS), diagnostic tests of interest (echocardiography and hemodynamic profiles), and intervention of interest (ventilator strategies, volume adjustment, pharmacological support and device therapy). Studies were included if they met the following criteria: (a) included patients with LoHF; (b) diagnosed using echocardiography and hemodynamic profiles; (c) treated patients for hemodynamic stabilization; and (d) reported treatment outcomes. In cases of studies reporting duplicate data, only the study that provided the largest number of patients was included. Conference abstracts, case reports and review articles were excluded.

Study selection

Figure 4 illustrates the search and screening process used to include eligible studies. Two reviewers independently screened all the titles and abstracts retrieved from the systematic online search. Abstracts that included population, intervention and outcomes of interest were included for full-text search. Afterwards, the two reviewers also independently reviewed full-text articles against the inclusion criteria. In cases of discrepancy, it was resolved through discussion and consensus.

Data collection

Two reviewers independently extracted data from the included studies and any discrepancy was resolved through consensus. The

main data extracted were echocardiographic and hemodynamic profile data, and treatment used and treatment outcome on hemodynamic (cardiac index, PCWP) and mortality. In addition to these main data, the two reviewers also extracted data on study characteristics, patients' characteristics and follow-up duration (Table 4).

Statistical analysis

Outcomes of interest reported in more than one study are cardiac index, PCWP and mortality. For each outcome, summary statistics (mean ± standard deviation) before and after intervention was extracted or the difference between baseline and after treatment. These summary statistics were extracted separately for treatment and control/placebo groups. Diagnostic outcomes and treatment effects were measured by difference in means before and after intervention and associated 95% confidence interval. Forest plots were used to visually examine heterogeneity (I^2) across studies. Pooled diagnostic and treatment effect and associated 95% confidence interval were estimated using fixed effect ($I^2 < 49\%$) or random effect model ($I^2 > 50\%$). P-value > 0.05 was considered statistical significant.

Results

Study characteristics

Twelve (12) randomized controlled trials (RCTs) satisfied the inclusion criteria. Seven (7) studies [63-67, 69,70] enrolled LoHF patients and the remaining five (5) [68,71-74] enrolled HF patients who have undergone cardiac surgery with low-cardiac output. The majority of published clinical trials (10) investigated medication comparing the effect of different types of inotropes on hemodynamic and prevention of death: dobutamine only [65], dobutamine and dopamine [63]; levosimendan and dobutamine [64,66-68,71], and levosimendan and placebo [72-74]. Of the remaining two clinical trials, each investigated vasodilator (nitroprusside) and placebo [69], and device therapy (IABP) and inotrope (levosimendan) alone or in combination with IAPB [70]. Altogether, the 12 clinical trials enrolled 3,738 patients, mean age 64 years (range = 55-74 years), with a majority being male (78%).

Synthesis of results

Diagnosis data on LoHF was inconsistent. Across the twelve clinical trials, no common definition of LoHF emerged that would have been
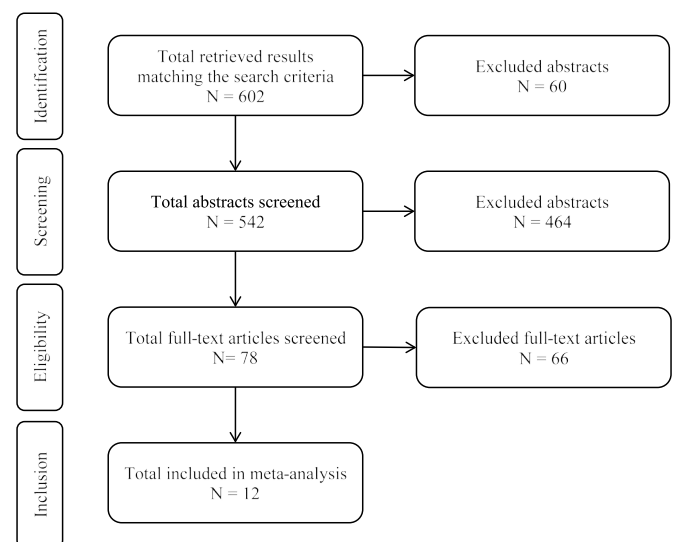
Figure 4. Flow diagram of literature search and inclusion process

Table 4. Summary of included studies

| 1st Author (year) [Ref #]	Type of treatment/ placebo	No. of Patients	Mean Age	Male (n)	Diagnosis criteria used in individual studies	Concluding remarks
Loeb et al. (1977) [63]	Dobutamine	8	58	8	Not reported	Both dobutamine and dopamine improve CO, but dopamine could elevate vascular resistance and LV filling pressure.
	Dopamine	5	58	5		
Follath et al. (2002) [64]	Dobutamine	100	60	85	LVEF < 35%; CI < 2.5 L/min/m²; PCWP > 15 mmHg	Levosimendan improved haemodynamic performance more than dobutamine and with lower 180-days mortality.
	Levosimendan	103	58	91		
Nishimura et al. (2002) [65]	Dobutamine	32	74	30	LVEF < 40%	Dobutamine challenge can aid in selecting patients who would benefit from an aortic valve operation.
Adamopoulos et al. (2006) [66]	Levosimendan	23	71	62	CI < 2.5 L/min/m²	Levosimendan improves better hemodynamic and LV function compared to dobutamine.
	Dobutamine	23	67	58		
Mebazaa et al. (2007) [67]	Levosimendan	664	67	493	LVEF < 30%; PCWP ≥ 18 mmHg; CI < 2.2 L/min/m²	Levosimendan did not significantly reduce 180-days all-cause mortality compared to dobutamine.
	Dobutamine	663	66	463		
Levin et al. (2008) [68]	Levosimendan	69	62	43	CI < 2.2 L/min/m²	Levosimendan proved more effective than dobutamine in improving hemodynamic and reducing mortality.
	Dobutamine	68	62	41		
Mullens et al. (2008) [69]	Nitroprusside	78	55	78	CI < 2.5 L/min/m²	Vasodilator plus optimal medical therapy has favourable long-term outcomes irrespective of inotropic support.
	Placebo	97	55	66		
Lomivorotov et al. (2012) [70]	IABP	30	57	29	CI < 2.0 L/min/m²; SvO₂ < 60% on minimal inotropic support	Infusion of levosimendan after anaesthesia in cardiac surgery improves haemodynamic compared with a preoperative IABP
	IABP/Levosimendan	30	58	29		
	Levosimendan	30	57	24		
Alvarez et al. (2013) [71]	Levosimendan	12	73	7	CI < 2.2 L/min/m²	Levosimendan vasodilates hepatic and portal venous system while dobutamine improve portal venous blood low.
	Dobutamine	13	72	6		
Cholley et al. (2017) [72]	Levosimendan	167	69	139	LVEF < 40%	In post-operative CABG levosimendan has no significant effect on preventing mortality compared to placebo
	Placebo	168	67	143		
Landoni et al. (2017) [73]	Levosimendan	248	66	159	LVEF < 25%; need for inotropic support	In post-operative CABG patients, levosimendan plus standard care did not lower 30-day mortality than placebo
	Placebo	258	66	168		
Mehta et al. (2017) [74]	Levosimendan	428	65	347	LVEF < 40%	Prophylactic levosimendan does not lower did not result in a rate of the short-term mortality compared to placebo.
	Placebo	421	65	332		

CI: Cardiac Index; **IABP:** Intra-aortic Balloon Pump; **LVEF:** Left Ventricular Ejection Fraction; **PCWP:** Pulmonary Capillary Wedge Pressure

useful to guide diagnosis. Hemodynamic criteria used for inclusion of patients in the trials included CI < 2.0 L/min/m² [70], CI < 2.2 L/min/m² [67,68,71] or CI < 2.5 L/min/m² [64,66,69] and PCWP > 15 mmHg [64] or ≥18 mmHg [67]. The definition also varied across studies – post-operative condition with hypotension (systolic BP < 90 mmHg for > 30 minute) or the need for inotropic support to maintain systolic BP > 90 mmHg and end-organ hypoperfusion (cold peripheries, urine output < 30 ml/hour) [70]. Cardiogenic shock has been described as a complex syndrome involving a cascade of acute LV dysfunction, decreased CO, hypotension and tissue hypoperfusion [67].

Figures 5 and 6 show forest plots for standardized mean of cardiac index at baseline and following inotrope or vasodilator therapy respectively. The baseline cardiac index increased from a mean of 1.93 (95% CI: 1.91-1.95) to post-treatment mean of 2.82 (95% CI: 2.80-2.84). Figure 7 shows a forest plot for standard mean difference (SMD) of cardiac index after treatment with levosimendan and dobutamine. Levosimendan achieve higher cardiac index compared to dobutamine (SMD: 2.82; 95% CI: 2.54-3.10). As a prophylactic against LoHF in post-operative patients, levosimendan infusion after anaesthesia achieved a higher cardiac index (2.57) compared to pre-operative IABP (2.3) or with a combination of levosimendan (2.4). Figure 8 shows a forest plot of mortality rate between levosimendan and placebo. Levosimendan had lower mortality rate compared to placebo (Odds Ratio [OR]: 0.83; 95% CI: 0.59-1.18) but the difference was not statistically significant (p=0.30). Final, Figure 9 further shows Levosimendan has a lower mortality rate compared to dobutamine (OR: 0.65; 95% CI: 0.39-1.08) but the difference was not statistically significant (p=0.10).

Discussion of findings

This systematic review and meta-analysis assessed common diagnostic features, and treatment outcomes of medical and device
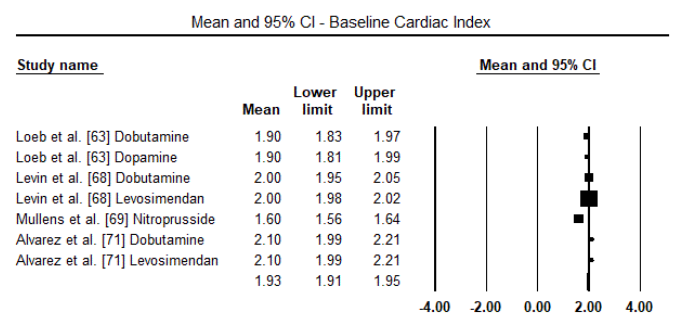
Figure 5. Mean baseline cardiac index
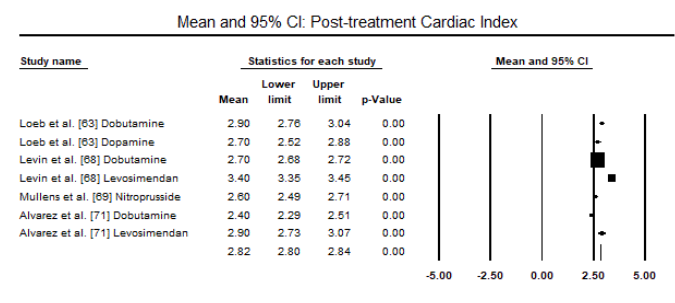
Figure 6. Mean post-treatment cardiac index

therapy (IABP) on LoHF patients. The results indicates that LoHF patients lack widely accepted or standardized diagnosis features. Although LoHF patients could exhibit several features including cardiac index, PCWP, systolic BP and SvO₂ to suggest or support clinical diagnosis, all these features have different cut-off values across
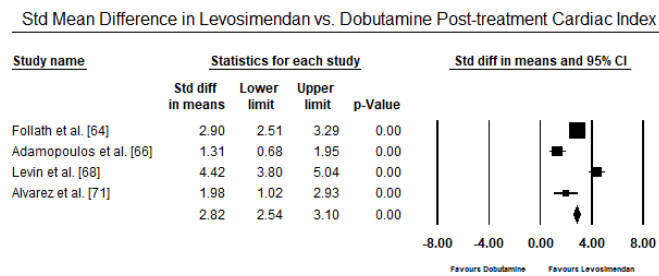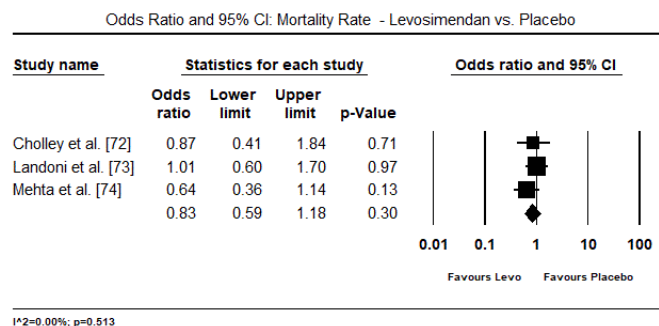
Std Mean Difference in Levosimendan vs. Dobutamine Post-treatment Cardiac Index

Study name	Statistics for each study				Std diff in means and 95% CI
	Std diff in means	Lower limit	Upper limit	p-Value	
Follath et al. [64]	2.90	2.51	3.29	0.00	
Adamopoulos et al. [66]	1.31	0.68	1.95	0.00	
Levin et al. [68]	4.42	3.80	5.04	0.00	
Alvarez et al. [71]	1.98	1.02	2.93	0.00	
	2.82	2.54	3.10	0.00	

-8.00   -4.00   0.00   4.00   8.00

Favours Dobutamine   Favours Levosimendan

Figure 7. Mean difference in cardiac index between levosimendan and dobutamine

Odds Ratio and 95% CI: Mortality Rate - Levosimendan vs. Placebo

Study name	Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-Value	
Cholley et al. [72]	0.87	0.41	1.84	0.71	
Landoni et al. [73]	1.01	0.60	1.70	0.97	
Mehta et al. [74]	0.64	0.36	1.14	0.13	
	0.83	0.59	1.18	0.30	

0.01   0.1   1   10   100

Favours Levo   Favours Placebo

I^2=0.00%; p=0.513

Figure 8. Mortality rate between levosimendan and placebo

Odds Ratio and 95% CI: Mortality Rate - Levosimendan vs. Dobutamine

Study name	Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-Value	
Follath et al. [64]	0.58	0.32	1.05	0.07	
Mebazaa et al. [67]	0.91	0.71	1.16	0.45	
Levin et al. [68]	0.29	0.10	0.78	0.01	
Alvarez et al. [71]	1.09	0.06	19.63	0.95	
	0.65	0.39	1.08	0.10	

0.01   0.1   1   10   100

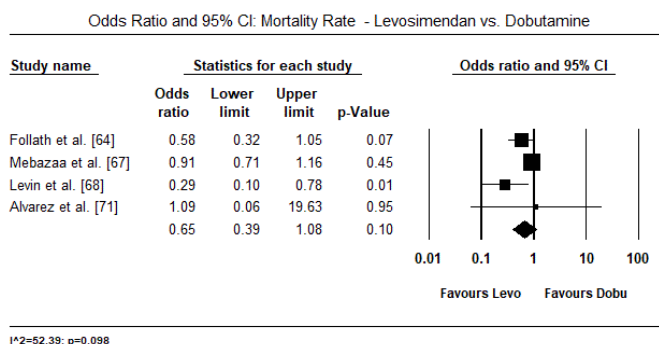Favours Levo   Favours Dobu

I^2=52.39; p=0.098

Figure 9. Mortality rate between levosimendan and dobutamine

studies. Cardiac index, which is the most common clinical feature demonstrating low-output state in LoHF, has three cut-off values: < 2.0 L/min/m² [70], < 2.2 L/min/m² [67,68,71] or < 2.5 L/min/m² [64,66,69]. Inotropic support emerged as a very common intervention for improving perfusion and normalizing cardiac output in LoHF patients.

Inotropic medication such as levosimendan, dobutamine, dopamine, vasodilator (nitroprusside) and IABP significantly improved CI between baseline and post-treatment. In terms of inotropes, levosimendan is more effective in improving hemodynamic stability and a better prophylactic against short-term death (30-day mortality) than dobutamine. In addition, inotropes can act as prophylactic against the development of post-operative LoHF. On the other hand, while inotropes improve hemodynamic and normalize cardiac output, they do not provide any significantly better protection against mortality irrespective of the type of inotrope used.

The role of inotropes in the treatment of LoHF has been supported by a previous review of inotropic agents and vasodilator strategies for the treatment of cardiogenic shock and LCOS [75]. The review reported inotropes improve hemodynamic, adverse events in post-operative

LCOS and reduced mortality. Newer inotropes such as levosimendan (a calcium sensitizer and inodilator) is a positive inotrope has some vasodilatory properties [67]. It can also be considered as a selective liver vasodilator, which can improve portal venous flow via hepatic artery and portal venous flow compared to dobutamine that can only improve portal venous flow without vasodilating the hepatic artery [71]. Levosimendan also does not increase myocardial oxygen demand and recommended over dobutamine in LoHF patients with acute myocardial ischemic or post cardiac surgery [5]. For post-operative LoHF, the protective effect of inotropes against short-term mortality rate (30-day mortality) remains insignificant compared to placebo [75].

The present systematic review and meta-analysis has some important limitations. LoHF may occur in secondary to underlying cardiac disease such as acute myocardial infarction or post-operative. Most of the studies included investigated post-operative LoHF with fewer presentation of LoHF from other causes. Most of the studies focused on two inotropes (Levosimendan and dobutamine), limiting the understanding of other inotropes as well as other therapies such as device therapies. In some trials, the analysis were at risk of misclassification bias due to a significant number of patients lost to follow-up. Since most of the trials do not report pair-wise pre- and post-intervention difference with associated standard deviation, pre and post-intervention difference with standard deviation, pre- and post-intervention outcomes measures as independent, this obtaining sider confidence intervals for treatment effect with an associated standard deviation.

Conclusion

Low-output heart failure (LoHF) is a clinical syndrome characterized by decreased cardiac output accompanied by end-organ hypoperfusion. It is an uncommon form of heart failure in the general population but prevalent in post-operation HF patients. Its aetiology is heterogeneous, consisting of various conditions causing low-output state and cardiac surgery. The main pathophysiologic mechanisms are LV systolic and/or diastolic dysfunction, and RV dysfunction caused by changes in heart rate, preload, afterload and/or contractility. General risk factors for LoHF include Chagas disease, depressed ejection fraction, and renal dysfunction while in post-operative patients include impaired LV function, incomplete revascularization, older age, and presence of diabetes and renal dysfunction. Diagnosis lacks standardized guidelines and dependent on accepted collection of hemodynamic and physiologic aberrations including conditions causing low-output state. Patient history and physical examination help to assess hemodynamic status and recognize low-output state while echocardiography confirms ventricular dysfunction (HF) and low cardiac output. Other tests to support diagnosis or establish the cause of low-output state include electrocardiogram and basic laboratory tests (blood, serum electrolyte, urea and creatinine, liver test, thyroid function and serum natriuretic peptides) and cardiac imaging (chest x-ray or coronary angiography). Treatment lacks established guidelines but depends on the assessment of individual pathophysiology to select the most appropriate treatment strategy. Treatment includes ventilator strategies to improve heart rate and rhythm; volume adjustment to optimize preload; pharmacological support (inotropes and vasodilators) to manipulate afterload and improve contractility; and device therapy (intra-aortic balloon pump or ventricular assist device) when these strategies do not restore cardiac output. In selected patients, therapies to reverse underlying disease, can restore cardiac output.

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