An investigation into the prehospital diagnosis, patient characteristics and treatment of cardiogenic acute pulmonary oedema (APO) patients: A scoping review

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LCKRUT001

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ABBREVIATIONS AND ACRONYMS

ACS: Acute coronary syndrome
AHF: Acute Heart Failure
ARDS: Acute respiratory disease
CAPO: Cardiogenic Acute Pulmonary Oedema
CCU: Coronary Care Unit
CHF: Chronic Heart Failure
CPGs: Clinical Practice Guidelines
dnHF: de novo heart disease
ECG: Electrocardiography
EMS: Emergency Medical Services
GTN: Glyceryl trinitrate
HAART: Highly active antiretroviral therapy
HIC: High Income Country
HIV/ AIDS: Human immunodeficiency virus/acquired immunodeficiency syndrome
HPCSA: Health Professions Council of South Africa
ICU: Intensive Care Unit
JVD: Jugular venous distention
LMIC: Low-middle-income country
MeSH: Medical subject headings
NCAPO: Non-cardiogenic pulmonary oedema
PBEC: Professional Board of Emergency Care
SBP: Systolic blood pressure
SCr: Scoping review

Part A: Background and Literature Review

Background

Acute heart failure (AHF) refers to abnormal cardiac structures or functioning resulting in inadequate or insufficient oxygen delivery by the heart. This may result in poor oxygenation of tissue cells, further creating imbalances in metabolisation, which, if left untreated, may lead to death. Comorbidities such as hypertension, diabetes, and coronary artery disease are all associated with acute heart failure [1,2]. Acute heart failure has a high mortality and morbidity rate affecting an estimated 26 million people worldwide; it is a global emergency. The 2017 Global Burden of Illness study found that 11.7 to 15.1% of deaths in this region were related to cardiovascular disease [3], although the incidence rate and prevalence of heart failure are still poorly understood in sub-Saharan Africa [4,5]. Furthermore, in most western settings, AHF is regarded as a disease affecting the elderly [6]. However, a recent increase in the prevalence of AHF among the younger patient population has been observed in sub-Saharan Africa [7]. Literature indicates that this might be associated with the use of highly active antiretroviral therapy (HAART) for those diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), which is, in itself, affecting younger populations in these settings [8].

Cardiogenic acute pulmonary oedema (CAPO), more specifically decompensated CAPO, is considered a severe subgroup of AHF. It is also a major contributor to this disease's high mortality and morbidity rates. Acute heart failure can best be described as the rapid onset and worsening of signs and symptoms of heart failure [6,9,10]. Cardiogenic acute pulmonary oedema can be caused by different mechanisms such as a disturbance in starling forces involving the pulmonary vasculature and interstitium (pressure-induced) [10,11] or the neurohormonal pathway. A disturbance in starlings forces results in excessive fluid accumulation in the alveolar walls and spaces of the lungs, resulting in laboured breathing. Ultimately, the patient presents with dyspnoea, and could present with hypoperfusion. At the point when the patient presents with dyspnoea, it is considered a life-threatening emergency requiring immediate assessment and intervention [9,12]. Additionally, if the patient presents with hypoperfusion additional interventions is required to address hypoperfusion and low cardiac output. Early administration of oxygen, vasodilators, diuretics, and continuous positive airway pressure ventilation are of high

priority could reduce the effects of these mechanisms. Patients presenting to prehospital emergency care providers with signs and symptoms representative of CAPO should thus be prioritised to receive rapid care because, much like acute coronary syndrome (ACS), recent literature indicates CAPO might have a ‘time to therapy’ concept [12,13,14]. Prehospital management is thus a critical component in CAPO patients’ diagnosis. However, it is often challenging to distinguish CAPO from other illnesses such as cardiomyopathy, hypertension, coronary artery disease, valvular stenosis, acute respiratory disease (ARDS), pulmonary embolism and viruses, such as dengue fever, which are also characterised by pulmonary congestion [4,15,16,17].

In the past, prehospital emergency care providers’ first-line treatment recommendations for CAPO patients involved a conventional approach, which included the administration of diuretics, opioids, and possible intubation (if hypoxia was not reversed by a non-rebreather face mask). However, a growing number of reports have since raised concerns about the dangers associated with this management strategy [13,18,19,20,21]. Among others, dangers associated with prehospital care ranged from electrolyte imbalance, diuretic resistance, hypoperfusion, hypoxia, hypotension, hypoventilation, or worsening renal functioning [13,18,19,20,21,22]. These dangers in combination with the effects of dyspnoea and a reduced cardiac output could further aggravate the depleted patient. These reports prompted a further investigation to gain a better understanding of AHF and, specifically CAPO, thereby also encouraging a review or change in guidelines for the prehospital management thereof. For some emergency medical services (EMS) – mostly those from high-income country (HIC) settings – changes in prehospital clinical practice guidelines (CPGs) for the management of CAPO improved outcomes for patients [20,21,22,23,24]. However, in low-middle-income country (LMIC) settings, such as South Africa, little is known about context-appropriate prehospital treatment approaches that would benefit those populations. This area is worth investigating to help emergency care providers follow a context-fit management approach in LMICs. It will likely reduce the potential negative outcomes associated with CAPO that is left unidentified and untreated.

Aim

The aim of this literature review was to provide an overview of existing literature surrounding the definition, diagnosis, past and proposed prehospital management recommendations for CAPO patients. The literature review aimed to establish a foundation for the proposed scoping review (SCr), reporting on evidence surrounding CPG for CAPO to be used by prehospital emergency care providers operating in LMIC settings.

Literature Review Objectives

The literature review:

- Defined AHF and CAPO
- Described the signs and symptoms of CAPO and its overall diagnosis
- Described past and proposed prehospital management recommendations for CAPO
- Described reported outcomes of prehospital management interventions for CAPO patients
- Contextualised the findings from the above objectives within an LMIC setting like South Africa

Search Strategy

An advanced Medline search was conducted via the PubMed database using the following medical subject headings (MeSH) relevant to CAPO in the prehospital setting:

((((acute decompensated heart failure) OR (Cardiogenic acute pulmonary edema)) OR (Sympathetic Crashing Acute Pulmonary edema) AND ((english[Filter]) AND (alladult[Filter]))) AND (((paramedic) OR (prehospital)) OR (emergency medical service) AND ((english[Filter]) AND (alladult[Filter])))) AND ((((management) OR (treatment)) OR (guidelines)) OR (recommendations) AND ((english[Filter]) AND (alladult[Filter]))) Filters: English, Adult: 19+ years, from 2010 – 2021.

The search was filtered into articles published and available in English print only and published between 01 January 2010 and 31 December 2022. The population was set to

only include literature dealing with adult patient groups above 18 years. No study design limitations were set.

Studies to be included in this literature review focused on:

- The epidemiology of CAPO
- The prehospital presentation and diagnosis of CAPO
- Historical prehospital management practices of CAPO
- Best practice recommendations for prehospital management of CAPO
- Overall relevance of the intended SCr investigation

Literature Review

Pathophysiology of Acute Heart Failure and Cardiogenic Acute Pulmonary Oedema

Heart failure is regarded as an abnormality of cardiac structures or functions, resulting in inadequate or insufficient oxygen being delivered to tissues [2]. Insufficient tissue oxygenation leads to imbalances in oxygenation and metabolization [4]. Heart failure may manifest as an acute episode, which means the symptoms have a sudden onset. Alternatively, it may manifest as a chronic episode where symptoms have a delayed onset [25]. Acute and chronic heart failure is characterised by a sequela of symptoms ranging from dyspnoea, pedal oedema, fatigue with associated signs of increased jugular venous pressure/distention (JVD), pulmonary adventitious sounds (crackles, rales, wheezes), and a possible displaced apex beat [10,25]. They can be defined by the onset of clinical symptoms, where AHF entails sudden onset with worsening symptoms compared to chronic heart failure (CHF), referring to the progression of symptom onset accompanied by multiple risk factors and comorbidities [4,25,26]. Acute heart failure warrants that all prehospital and in-hospital emergency care providers cooperate in rapid patient treatment [25,27].

The clinical manifestation of pulmonary oedema in AHF often causes patients to become dyspnoeic and consequently fatigued. This is because pulmonary oedema is brought about by the excessive accumulation of fluid within the alveolar wall and spaces in the

lungs, increasing the work of breathing and limiting oxygenation [10]. Pulmonary oedema, if left untreated, becomes a serious life-threatening emergency in some patients [10,28].

Pulmonary oedema can be either cardiogenic or non-cardiogenic in origin [10]. Cardiogenic acute pulmonary oedema is attributed to disturbances of starling forces, whereas non-cardiogenic pulmonary oedema results from direct injury to the lung parenchyma [29,30]. Starling's forces are one of the drivers of pulmonary oedema, however, the neurohormonal pathway is another driver of pulmonary oedema as it plays an important role in disease severity and the mediation of heart failure. In patients with heart failure, a reduction in cardiac output caused by cardiovascular injury could lead to a reduction in ejection fraction, this combination causes the unloading of high-pressure baroreceptors in the left ventricles, aortic arch, and carotid sinuses. Neurohormonal activation includes the collective response of the sympathetic nervous system and the Renin-Angiotensin-Aldosterone System (RAAS), causing the maintenance of cardiac output by increasing such as salt, the retention of water and peripheral arterial vasoconstriction and increasing contractility and inflammatory mediators. The increase in sympathetic nervous system activity in the kidneys results in the activation of arterial and venous constriction. This results in pulmonary and peripheral oedema, characterizing worsening heart failure. [29,30] Furthermore, CAPO is attributed to any factor that increases the pressure and pooling of blood on the left side of the heart [29]. Conversely, non-cardiogenic pulmonary oedema (NCPO) is resultant of direct damage to the parenchyma and vasculature of the pulmonary system.

It is important to differentiate between CAPO and NCPO as management changes based on the cause [10,14,29]. However, in the prehospital setting, it is often challenging to distinguish between the two and difficult to diagnose the presence of CAPO as the cause of pulmonary congestion. This may lead to the underdiagnosis of CAPO patients, and subsequent mistreatment [4,31,32,33].

Clinical assessment findings of cardiogenic acute pulmonary oedema versus non-cardiogenic pulmonary oedema

Patients with CAPO can, among other complications, experience symptoms of excessive dyspnoea that are worsened on exertion or laying down. They can also present with cold and clammy skin and blood-tinged/pink-coloured frothy sputum in very severe cases. One of the main clinical examinations to be performed is done to identify the severity of CAPO, characterised by the patient's hemodynamic status. One method of assessing hemodynamic status is measuring the patient's blood pressure. Cardiogenic acute pulmonary oedema can either present as 1) normotensive CAPO, where the blood pressure is unchanged or appear normal for the patient's weight and age, 2) compensated CAPO, where there is a rise in blood pressure, often referred to as hypertensive CAPO, or 3) decompensated CAPO, which is a state of cardiogenic shock resulting in hypoperfusion [4,10,28].

Epidemiology of Cardiogenic Acute Pulmonary Oedema

In 2009, the prevalence of AHF syndromes was approximately 5 800 000, accounting for 2% of the entire populace, with an estimated 75 000 to 83 000 cases per 100 000 patients diagnosed with Acute Pulmonary Oedema in the United States of America (USA) [29,34,35]. Over the years, the number of patients hospitalised for AHF syndrome grew exponentially in the USA and Europe, where an annual incidence rate of 2.5 per thousand inhabitants has been reported [25,36]. Additionally, statistically, the number of patients dying during admission is double those dying one year after an episode [37,38,39,40,41,42]. Furthermore, decompensated CAPO, as mentioned, is on the severe clinical spectrum of AHF, with a prevalence rate of 10-20% in unsettled AHF patients [5]. Studies have shown that admission to hospital with decompensated CAPO is an independent risk factor for poor patient outcomes [43,44,45].

Reported data on the burden of AHF remains low in South Africa [27], and data from LMIC settings cannot be relied upon as a true representation of the occurrence of AHF, more specifically CAPO [27,46,47]. Underreporting can also be multifactorial in LMIC settings; for one, CAPO can be underdiagnosed since it is challenging to diagnose and differentiate

from NCPO in the prehospital setting [4,31,32,33]. It can also be inappropriately triaged, and such patients may be transported to facilities that do not comply with reporting requirements. Consequently, misdiagnosis and underdiagnosis of CAPO in LMIC settings may potentially mean that mortality and morbidity rates related to the illness are higher than those in HIC settings [6,48].

Furthermore, while AHF is a disease considered to mostly affect the elderly in western countries, in the sub-Saharan setting, literature identifies that AHF is predominantly affecting the young patient population [47]. Research highlights that AHF being common among this group can be associated with the use of HAART for those diagnosed with HIV/AIDS, which is currently affecting many younger populations in sub-Saharan Africa [8,47]. In addition, other diseases such as hypertension and tuberculosis are also impacting the young patient population group, and these diseases have been described as contributing factors in developing new diagnoses of heart failure “de novo heart disease” (dnHF) [34,49].

Prehospital Management and Cardiogenic Acute Pulmonary Oedema Outcomes

Prehospital emergency care providers are usually regulated and guided by professional bodies. This is done to protect the public by establishing contextually relevant standards for healthcare training and practices. The professional body typically provides CPGs to healthcare professionals to optimise patient care. In South Africa, the Health Professions Council of South Africa (HPCSA) Professional Board of Emergency Care (PBEC) is the regulating body for prehospital emergency care providers.

Over the last three decades, EMS in South Africa has evolved from the traditional rapid transportation with limited to no treatment approach toward a more structured evidence-based care approach for victims of sudden and life-threatening injuries or emergencies, aiming to prevent needless mortality or long-term morbidity [50,51,52]. In 2016, a CPG was developed, informed by a systematic review of evidence and the identification of risks and benefits of alternative care options, to help facilitate this more structured, evidence-based approach for prehospital emergency care providers [51]. As mentioned, diagnosing

and treating CAPO is a priority, and the emergency care provider thus plays a pivotal role in CAPO patients' health outcomes [50,51].

Since the CPG in South Africa has changed and been updated, many registered emergency care providers are either outdated in their scope of knowledge and skills, while others might be aware of the 2018 CPG recommendations in the management of AHF and are following these guidelines. However, since the CPGs were adopted from international literature, where the proposed AHF management strategy has been validated, the possibility remains that the currently proposed CPG on AHF management, more specially CAPO, is not context-appropriate for the South African setting. It would therefore be important to critically review international AHF recommendations and identify possible challenges to its adoption in contexts like South Africa. Moreover, it is also important to take a historical look at the past prehospital treatment recommendations for AHF to understand why NIV, CPAP, and nitrates are used, with less emphasis on the use of furosemide and morphine as first-line treatment, since some emergency care providers are possibly still following the old recommendations, which may impact patient outcomes negatively.

Past Prehospital Management Strategies for AHF and Cardiogenic Acute Pulmonary Oedema

In the past, the CPG treatment recommendation was a conventional treatment strategy that involved the administration of high-dosage opioids and diuretics as a first-line drug agent, and face mask oxygenation or intubation if face mask oxygen was insufficient [51]. However, over time, published literature started to highlight several dangers associated with this treatment regime, specifically in the administration of opioids and diuretics without optimal oxygenation [20,22]. The dangers included electrolyte imbalances, diuretic resistance, hypoperfusion, hypoxia, hypotension, hypoventilation, or worsening renal function [53,54,55].

Administration of Diuretics such as Furosemide

The use of high-dose diuretics (1-2mg/kg) for patients presenting with CAPO is no longer advocated as a first-line treatment modality. Previously, it was administered in order to prevent ventilation/perfusion mismatches when there was evidence of systemic "fluid overload" [20,56,57]. However, with reference to CAPO's pathophysiology, these patients have a decrease or lack of intravascular volume, and diuretics could have negative effects as it reduces preload [58]. Furthermore, the effects of high-dose diuretics can result in diuretic resistance, electrolyte imbalance, and worsening renal function, potentially causing hypoperfusion, hypoxia, hypotension, and hypoventilation [53,54,55,59].

Administration of Opioid Morphine

Historically, the administration of morphine in CAPO patients was assumed to improve oxygenation due to vasodilation, which subsequently reduced cardiac preload. In addition, morphine also acted as an anxiolytic, considered beneficial in dyspnoea. However, recent literature advises that morphine has delirious effects, which include respiratory and central nervous system depression [14,60,61]. These effects have the potential to exacerbate the condition and worsen the prognosis by causing a severe decrease in cardiac output and producing significant hypotension [13,21,57]. Furthermore, published literature highlights that the routine use of morphine for patients with CAPO increases the length of hospital stays, hospital readmission, the need for mechanical ventilation, and mortality rates [13,18,21,28,57]. In addition, opioid administration in patients with CAPO can result in worsening symptoms such as bronchoconstriction leading to hypoxia or hypoventilation, deteriorating renal functions caused by urinary retention/resistance, and electrolyte disturbances [13,18,21,28, 53,54,55,57].

Administration of Glyceryl Trinitrate (GTN)

The previous 2006 HPCSA PBEC practice guideline recommended the administration of glyceryl trinitrate (GTN) for the management of pulmonary oedema. The dosage was one of 0.4mcg per sublingual tablet or sublingual spray on the oral mucosa to a maximum of three sprays. Systolic blood pressure (SBP) should be monitored while administering the

medication, and the treatment should be terminated in the following instances: >10% decrease of SBP in normotension, >30% decrease of SBP in hypertension, and when SBP <90 mmHg. The dangers associated with the administration of GTN for pulmonary oedema relate to CAPO's pathophysiology. Consequently, the administration of high doses of GTN may result in arterial relaxation, a reduction in afterload, cardiac output, and blood pressure [24,62,63,64,65].

The way forward

The incidence of heart failure accompanied by decompensatory cardiogenic shock increases the risk of congestive heart failure mortality by 85% within six years [12,29]. Together, this high mortality rate, accompanied by the harmful effects of previous prehospital treatment regimens, instigated further investigation [66]. First, this prompted a better understanding of decompensatory CAPO. Second, this also encouraged a review of CPG recommendations for its management, as it was believed the practice guidelines were outdated and potentially less effective (possibly posing more negative outcomes) [65,67].

Evidence-based Recommendations for the Management of Cardiogenic Acute Pulmonary Oedema and its Context Appropriateness in EMS Settings Such as South Africa

Acute heart failure was proven to be a time-sensitive emergency requiring aggressive investigation and intervention [54]. As a result, several HIC settings have since revisited and updated their prehospital CPG recommendations for the treatment of CAPO [23,24,58,68,69]. These changes were based on evidence-based recommendations.

In reviewing previous AHF management practices, published literature highlighted concerns about the 'one size fits all' approach to the prehospital management thereof [70]. This was clearly linked to the use of the term 'AHF', disregarding the different clinical characteristics with which AHF may present to the emergency care provider [12,56]. Recommendations thus started to reveal AHF require a common working definition; a definition that would include all the dimensions and patient presentation mode [12], as the

most common attributes of the presentations is an acute onset of dyspnoea that is associated with an increased blood pressure or the compensation of underlying chronic heart failure. Also, at presentation, most CAPO patients are normotensive or have high blood pressure, which is somewhat contradictory to the belief that low cardiac output necessarily leads to symptomatic hypotension and signs or symptoms of hypoperfusion (decompensated CAPO) [59]. Decompensated CAPO, although rare, is associated with poor outcomes [4]. Therefore, early identification and treatment using appropriate therapy would be required in the specific AHF phenotype, and would prompt urgent treatment [34,54].

First, in updating the CPG, the term 'heart failure' was further classified using a more descriptive name to assist with the desired outcome. Acute heart failure was classified as; a) non-cardiogenic acute pulmonary oedema, b) cardiogenic acute pulmonary oedema - normotensive, c) compensatory cardiogenic shock, and d) decompensatory cardiogenic shock [4,29]. The CPG therefore categorises patients according to their pathophysiological presentation of AHF, which concerns SBP, among other signs and symptoms. It is believed that these classifications could facilitate rapid risk stratification, and thus assist with clinical decision-making and patient disposition [15,54,72,73].

Second, since CAPO is associated with high mortality rates [74], early identification, appropriate treatment and disposition in the prehospital setting could be one way of improving the prognosis of the disease. Prehospital identification of pulmonary oedema caused by low-risk conditions could offer several benefits to poorly resourced settings. EMS will be able to refer patients at lower risk to less resource-intensive facilities, leading to a reduction in healthcare visits and costs [75]. In addition, scant resources can be availed for emergencies since alternative transportation can be provided to low-risk patients. Published literature has thus indicated that prehospital treatment plans for patients presenting with pulmonary oedema should be guided by risk stratification since the identification of high-risk patients in the prehospital setting has proven to be challenging [76,77]. However, most proposed risk stratification tools incorporate the use of biomarkers, point-of-care ultrasound examinations, non-invasive blood pressure

monitoring, capnography, or 12-lead electrocardiography (ECG) assessments [73]. Often, these tools are either unavailable in poorly resourced settings, like many health facilities and provincial EMS in South Africa, or personnel lack the experience or knowledge to make use of these tools as it does not form part of their scope of practice.

Following risk stratification, literature proposes the implementation of tailor-made treatment approaches according to risk stratification findings [15,54]. As seen in Figure 1, these treatment goals are categorised into; a) symptomatic relief, b) improvement of oxygenation, c) maintaining cardiac output, d) ensuring the perfusion of vital organs, and e) reducing excess extracellular fluid accumulation [25].

Figure 1: *Clinical profiles of patients with AHF based on the presence or absence of congestion and/or hypoperfusion. Adapted from the 2016 ESCC guidelines on acute and chronic heart failure*

Finally, together with early identification and management of CAPO, a referral pathway is considered a priority for the continuation of care and improved patient outcomes [61].

Despite improvements in long-term care for AHF in recent decades, hospital and long-term death rates related to AHF are still high. This is potentially linked to the fact that AHF is difficult to identify because of numerous clinical scenarios, and AHF might present in the presence of several other comorbidities [78]. Literature identified that an improvement

of the prognosis of AHF requires new effective drugs or devices and an analysis and improved course of care for such patients. This would ideally promote to establish an optimal course of care across the healthcare sector [4,26,79].

Different healthcare providers are involved in AHF patients' clinical pathways across the globe. With regards to the prehospital setting that provides emergency care, countries such as South Africa and Australia have established what is known as three-tiered EMS systems [80]. In these healthcare systems, EMS consists of emergency care providers, also often referred to as paramedics, who offer basic, intermediate, or advanced life support depending on their qualifications and subsequent scope of practice. Treatment commences within the prehospital setting, and these patients should preferably be transported to the most appropriate facility for care optimisation and continuation. In other, mostly European, countries like Germany and the Netherlands, two-tiered EMS structures are found [80]. These healthcare systems contain EMS, which consists of basic and intermediate care responsible for stabilising patients, and prehospital physicians who initiate advanced critical care if needed.

In one prospective observational cohort study in France [81], researchers aimed to describe AHF patients' from the initial medical contact care through hospital discharge, and analyse its influence on outcomes and prognosis after hospitalisation. That study found no significant association between the care route and patient prognosis. However, the study did find that a cardiologist's intervention in the management of AHF patients might shorten their hospital stay and rates of readmission. The study thus proposed mobile AHF cardiology teams for the prehospital setting. In addition, it hypothesised that AHF cardiology teams in each hospital would be as beneficial as transportation to a cardiology department. Similar findings were reported in another multicentric cohort study, also conducted in France [42].

A foreseeable challenge in poorly resourced settings concerns the continuation of optimal care provided to AHF patients from prehospital to in-hospital patient handover. First, South Africa lacks a universal healthcare system; instead, the healthcare system consists

of two systems operating in tandem with one another, namely a private healthcare system and a provincial healthcare system [82].

The provincial healthcare system is funded by the state, and it is typically underfunded. This creates challenges in healthcare service delivery since 80% of the population is dependent on the provincial healthcare system [83,84,85]. Consequently, there are resource-limited hospitals with limited cardiac departments and coronary care units (CCUs), but also limited bed space. In the provincial healthcare sector, one medical specialist serves around 11 000 patients [86]. The Western Cape, Gauteng, and KwaZulu-Natal provinces have the most ICU beds available for patients relying on provincial health care [83], while other provinces, such as the Free State, Limpopo and the Northern Cape have lower ICU bed capacity. Nationally, 75% of ICU bed availability is accounted to the private healthcare sector in South Africa, whereas the remaining 25% account for the public healthcare sector beds [83]. The resources and healthcare expenditure in the private sector is ten times more per capita than that reported for the public sector, indicating that the private sector is better resourced than the public sector [82,87]. In addition, there is one medical specialist in the public sector for every 500 patients [82]. Moreover, the public healthcare sector only contains 20-30% of the country's cardiology resources [88]. This is indicative of the stark differences in resource allocation, skills, and expertise across the healthcare system to offer cardiovascular care. As a result, South Africa still has a long way to go, since the best practice course pathway for AHF patients should include an available cardiologist during initial management.

Second, since a nationally approved referral policy is lacking in South Africa [90], the current referral pathway in provincial EMSs in different provinces varies. Various levels of hospitals are defined by their package of services in each province. Also, a hierarchical relationship exists between these hospitals, as outlined in Table 2.

Table 2: Classification of hospitals

DISTRICT HOSPITAL	REGIONAL HOSPITAL	TERTIARY HOSPITAL	CENTRAL HOSPITAL	SPECIALISED HOSPITAL
Serves a defined population within a health district and supports primary healthcare	Between 200 and 800 beds	From 400 to 800 beds	Maximum of 1 200 beds	Maximum of 600 beds
Provides a district hospital package of care on a 24-hour basis	Offers services to a defined regional drainage population, limited to provincial boundaries	May provide training for healthcare service providers	Must provide training for healthcare providers; conduct research; and must be attached to a medical school as the main teaching platform	
Have general practitioners and clinical nurse practitioners who provide primary health services	Receives referrals from several district hospitals; provides short-term ventilation in a critical care unit; and, where practical, provides training for healthcare service providers	Receives referrals from regional hospitals not limited to provincial boundaries	Receives patients referred to it from more than one province	Receives patients referred to it from other levels of care
May only provide the following specialist services: (a) paediatric health services, (b) obstetrics and gynaecology, (c) internal medicine; (d) general surgery;	Provides health services in the fields of internal medicine, paediatrics, obstetrics and gynaecology, and general surgery; and at least one of	Specialist-level services provided by regional hospitals; provides intensive care services under the supervision of a specialist or specialist intensivist	Provides tertiary and central referral services and may provide national referral services	Provides specialised health services like psychiatric services, tuberculosis services, infectious diseases and rehabilitation services

DISTRICT HOSPITAL	REGIONAL HOSPITAL	TERTIARY HOSPITAL	CENTRAL HOSPITAL	SPECIALISED HOSPITAL
and e) family physician	the following specialities, namely orthopaedic surgery; psychiatry; anaesthetics; diagnostic radiology; trauma and emergency services			

Source National Department of Health, Regulation R185

Specialist and sub-specialist services are provided in specialised, regional (level 2), tertiary (level 3), and central (level 4) hospitals (Regulation R185). From district hospitals, patients are referred to regional hospitals and then to provincial tertiary hospitals. Depending on the care and intervention required (Figure 2), patients are further referred to national referral hospitals and central hospitals [90].

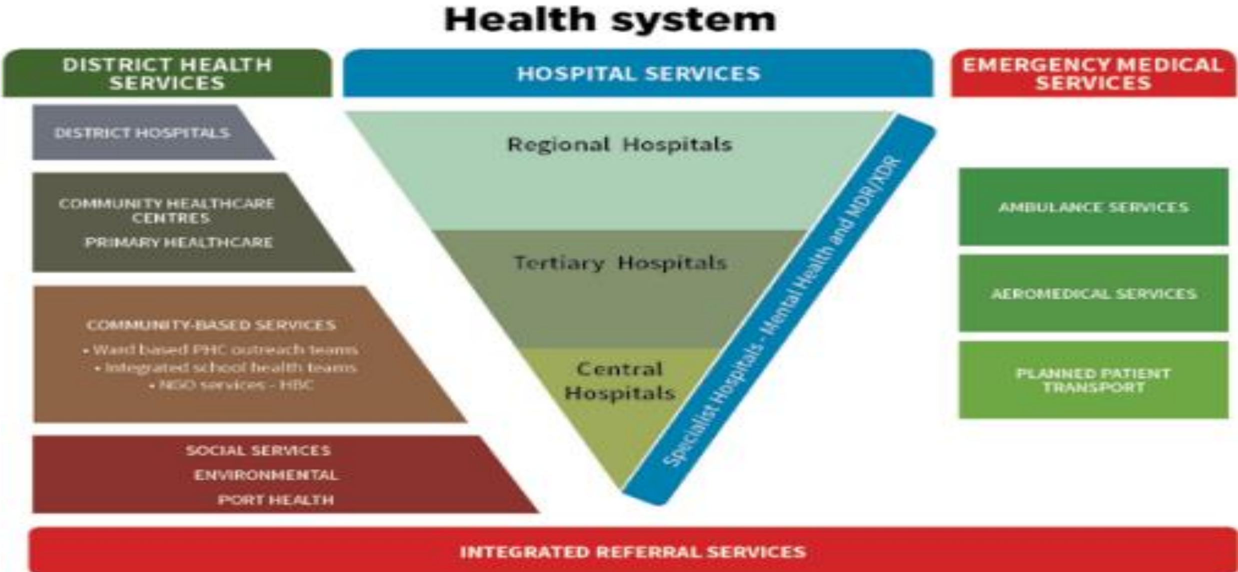

Figure 2: *Services across different levels within Health Service Delivery Platform*

Within the Cape Metropolitan Region (Cape Metro) in the Western Cape Province, EMS initially transports primary callout patients to either district or regional hospitals within a specific catchment area. Only once the patient is triaged and seen at these facilities are they referred for specialist care at a tertiary hospital as and when needed. This referral is also dependent on bed and specialist availability at the referral facility at the time of referral. One of the many reasons this referral pathway was incorporated was to alleviate pressure on tertiary hospitals, which are perpetually limited in resources. Although there are benefits to this referral pathway, it does generate new challenges elsewhere. For example, the referral pathway places strain on an already burdened EMS system, where advanced care providers, which are limited in number, are redirected from primary callouts to attend to interfacility patient transfers, which often take several hours to complete. In addition, from an AHF management point of reference, there is a delay in cardiologists becoming actively involved in patient care.

The researcher is therefore of the view that it is very unlikely that South Africa will be able to accommodate the recommendations for either EMS transportation for AHF patients directly to a facility with a cardiologist in place; or the creation of mobile cardiology teams available for patients in the prehospital setting. However, there might be room to incorporate the recommendation to develop cardiology teams at different facilities. These cardiology teams can consist of non-expert task-sharing providers (role extension) who have undergone specific training in this area [3]. As an alternative, public-private partnerships might also be of benefit since the public healthcare sector lacks resources compared to private healthcare capabilities and resources [91,92]. Similarly, although there are other evidence-based recommendations for the prehospital management of AHF, to the researcher's knowledge, it is not known whether these recommendations can holistically be adopted within LMIC settings. However, more context-relevant strategies may be employed as alternative solutions in the management of AHF by prehospital emergency care providers [3,93]. A SCr to examine the current evidence base surrounding CAPO management recommendations for prehospital emergency care providers will be of benefit; specifically, focusing on whether there will be specific

challenges in LMIC settings, and if so, finding alternative strategies best suited for the LMIC setting.

Summary

The literature review highlights past and current AHF emergency care recommendations based on evidence-based practices, demonstrated through research conducted in mostly HIC settings. This review also highlights the potential challenges that a country such as South Africa may face in adopting some of these recommendations. A SCr would seem the ideal tool to identify and review published literature on CAPO management recommendations for emergency care personnel specifically in the LMIC context. In so doing, the researcher intends to highlight potential challenges associated with each proposed AHF management priority.

It is believed that a SCr will accomplish this, Munn et al. [94,95] suggest that a SCr can map out and report different types of evidence useful to direct and inform practice in the field. In this instance, the SCr will specifically look at the contexts in which AHF management recommendations were investigated and adopted. These include reviewing and reporting on the nature of how research was conducted; whether the setting is considered well-resourced or poorly resourced; the healthcare structure; the type of emergency care providers in relation to their years of education and scope of practice; as well as factors that influence correct diagnosis and good outcomes among CAPO patients. In addition, the SCr is also useful for identifying potential challenges in the implementation of CAPO best practice recommendations in LMIC settings. To find any gaps in the literature, these challenges will be contextualised to the prehospital setting in South Africa. In addition, the researcher wants to review the published literature to identify alternative strategies that might be more context-appropriate in the prehospital management of CAPO in poorly resourced settings.

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An investigation into the prehospital diagnosis, patient characteristics and treatment of cardiogenic acute pulmonary oedema (APO) patients: A scoping review

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Abstract

Introduction:

A scoping review was conducted to identify current clinical practice guidelines for the diagnosis and treatment of cardiogenic acute pulmonary oedema (CAPO) in the prehospital setting and the application and relevance of these findings for low- to middle-income countries (LMICs). Specific practice guideline elements, including clinical presentation, timely diagnosis, triage, recommended treatment, and clinical referral pathways, were reviewed.

Methods:

Published literature was systematically searched using the framework developed by Arksey and O'Malley. Using a priori-developed search strategy, electronic searches were performed in PubMed, Africa Wide, Scopus, Medline, and CINHAL databases to identify articles published in English between 2010 and 2022 relevant to CAPO in the prehospital setting. Two authors independently assessed whether each article met one or more of the four inclusion criteria, with disagreements resolved through either a discussion or adjudication from a senior reviewer. A summary of the main themes from all eligible articles was developed using descriptive analysis.

Results:

A total of 1193 articles were identified. In the screening process, 13 were duplicates and were removed, and 1061 articles were removed based on the title and abstract review. After a full-text review was conducted to determine eligibility, 83 articles were removed. Ultimately, 35 articles meeting the inclusion criteria were included for final review and analysis. The following three themes were identified during the analysis: clinical presentation of CAPO and prehospital diagnosis; prehospital management and care; and referral pathways that facilitate better patient outcomes.

Conclusion:

The review highlighted key information for risk-stratifying CAPO patients to guide patient-centred care and transportation decision-making. Most of the published literature

discovered in this scoping review was published from high-income country (HIC) settings, which reflects the gap in evidence on best practice recommendations that are context-fit for LMICs. Implications for LMICs are discussed.

African Relevance:

- This article describes current published literature on clinical practice guidelines for CAPO in the prehospital setting, identifying possible gaps in knowledge and implementation.
- There is a lack of context-appropriate evidence-based recommendations for the prehospital management of CAPO in resource-limited settings.
- This article provides insight into the prehospital diagnosis and management of CAPO within resource-limited settings to facilitate better patient outcomes.

Keywords:
Cardiogenic Acute Pulmonary Oedema; Decompensatory Cardiogenic Pulmonary Oedema; Acute Heart Failure; Prehospital setting

Introduction

Heart failure is a life-threatening illness and has been viewed as a global health priority [1,2,3,4,5]. Managing patients with heart failure places great demands on healthcare systems due to an increase in prevalence rates, accompanied by an ageing population [6,7,8,9]. It can also be costly for the patient and the healthcare system to manage heart failure as it often requires a high level of medical intervention. The cost of heart failure management could thus overload the healthcare system in resource-limited countries already burdened with diseases [7,9,10,11,12]. Globally, there has been a stark increase in the prevalence and mortality of cardiovascular diseases and heart failure in low to middle-income countries (LMICs) compared to high-income countries (HICs) [6]; however, research remains scarce regarding the classification and management of heart failure in LMICs [7].

Heart failure symptoms either manifest with a sudden onset, referred to as acute heart failure (AHF), or the symptoms may have a more insidious and delayed onset, referred to as chronic heart failure (CHF) [14]. In resource-limited countries like South Africa and sub-Saharan Africa, an increase in diseases such as hypertension and HIV has been observed among younger adult age groups, posing a risk of cardiovascular disease and heart failure [15,16,17]. This increased prevalence is thought to be multifactorial and poses a challenge in the diagnosis and treatment of heart failure. Contributory factors include a shift in lifestyle behaviour, socioeconomics, poverty, infectious diseases, lack of adequate resources, lack of equipment and inaccessibility to quality healthcare [9,17,18,19].

AHF has a high mortality and morbidity rate and has affected approximately 26 million people worldwide. It is caused by numerous factors, such as ageing populations, variations of aetiologies, clinical characteristics or treatment modalities [20]. Cardiovascular and non-cardiovascular disease conditions increase the risk of mortality from 25% to 30% after 60- to 90-day rehospitalisation. In AHF, short-term mortality rates at 30-day and 180-day account for 2.6% and 11.3%. Furthermore, the 7-day mortality rate factor is high for patients arriving at the hospital by ambulance with a poor prediction of outcomes. Patients presenting to the hospital by ambulance appear to have a higher mortality rate than self-presenting patients. This could be multifactorial as these patients could be more educated about their symptoms and when to contact an ambulance, which could be related to disease severity. Among patients with AHF, the mortality rate increases by 17% to 45% within the first year after diagnosis. Astonishingly, it is estimated the majority of patients will die within five years of diagnosis, indicating the poor outcomes for patients with heart failure [9,21,22,23,24]. AHF thus warrants that all prehospital and in-hospital emergency care providers cooperate in providing care and optimising patient outcomes [14,25]. However, in LMICs, there is a discord in presentation, diagnosis and treatment, which is challenging when developing optimal healthcare treatment modalities [7,26].

Cardiogenic acute pulmonary oedema (CAPO), specifically decompensated CAPO, is considered a severe subgroup of AHF and is a major contributor to the currently observed high mortality and morbidity rates attributed to this disease [27,28]. CAPO is caused by disturbances in starling forces involving the pulmonary vasculature and interstitium [29]. This results in the accumulation of excessive fluid in the alveolar walls and alveolar spaces of the lungs, which makes it difficult for the patient to breathe. Ultimately, the patient may present with dyspnoea and signs suggestive of hypoperfusion, which warrants immediate assessment and intervention [28,31].

Patients presenting to prehospital emergency care providers with signs and symptoms of CAPO should be prioritised to receive rapid care. This is because, much like acute coronary syndrome (ACS), recent literature indicates that CAPO might have a 'time to therapy' concept [31,32,33]. Prehospital management is thus a critical component in the management of CAPO patients. However, it is often challenging to distinguish CAPO from other illnesses such as cardiomyopathy, hypertension, coronary artery disease, valvular stenosis, acute respiratory disease (ARDS), and pulmonary embolism, among others, which are also characterised by pulmonary congestion [21,34,35,36]. Compliance with clinical practice guidelines that provide evidence-based recommendations for the prehospital emergency care provider's treatment of emergency conditions is an important element in facilitating improved outcomes for emergent conditions like AHF. Still, several evidence-based recommendations for the prehospital care of AHF are not context-appropriate for the resource-limited prehospital setting.

According to the authors' knowledge, no published literature was available that holistically addressed evidence-based recommendations on prehospital care for AHF, from prehospital patient presentation, diagnosis and management, to patient handover. The authors therefore set out to scope and review published information on the prehospital presentation, diagnosis, management, and clinical referral pathways of AHF patients. The goal was also to contextualise the information to prehospital care within resource-limited settings. Ultimately, CAPO is an emergency requiring immediate diagnosis, treatment,

and appropriate disposition, yet it is challenging to implement practice guidelines in resource-limited countries, both in the prehospital and in-hospital settings.

Method

Given the limited knowledge in this research area and broad research questions, a scoping review was thought to be the most appropriate research methodology. This scoping review used the framework developed by Arksey and O'Malley [37], which was further refined by Levac Colquhoun and O'Brien [38]. This review also adhered to the Preferred Reporting Items for Scoping Reviews and Meta-analysis extension for Scoping Reviews (PRISMA-SCr) [39].

The scoping review questions were formulated based on the three essential stages of care outlined in the European Society of Cardiology's Global Heart Failure Awareness Programme [9]. This programme, essentially developed to guide in-hospital care for heart failure, specifically outlined a comprehensive approach that includes the application of best practices in three essential stages of care: diagnosis, treatment, and long-term management.

The scoping review thus sought to answer the following research questions:

1. What is the prehospital clinical presentation of AHF, and what assessments are appropriate for accurate and timely diagnosis and triage?
2. Which prehospital management recommendations are appropriate for AHF?
3. What recommended clinical referral pathway may facilitate optimal patient outcomes?

All scoping review questions and their findings were further contextualised for appropriateness in the resource-limited prehospital setting in LMICs based on direct experience. The primary objective of the study was CAPO; however, search terms and reviewed literature include AHF intending to identify potential overlapping and applicability towards CAPO.

Studies were contextualized using a consensus approach amongst researchers, assessing applicability of studies after review. Studies were reviewed by their background, study setting, location, and the expert experience.

Search criteria

PubMed, Africa Wide, Scopus, Medline, and CINHAL online databases were used to identify relevant peer-reviewed research articles to help address the research questions. A search of all databases was conducted using the search terms "acute heart failure", "emergency medical service" and "clinical practice guidelines". To address the research questions, a comprehensive search strategy was compiled using these terms. (Appendix A).

Study selection: Inclusion and exclusion criteria

All retrieved articles were imported into Mendeley Desktop (Version 1.19.4, Mendeley Ltd., London, United Kingdom) for storage and removal of duplicates (RL). The author (RL) used the eligibility criteria to conduct a first-level screening of titles and abstracts. Potentially relevant literature was identified by retrieving full papers.

Two reviewers (RL and CG) independently assessed whether each of the full-text articles satisfied one or more of the four inclusion criteria: 1) is the article about emergency medical service (EMS) or prehospital emergency care; 2) is the article about best practice recommendations for CAPO management and, if so, is there a direct overlap with criteria #1; 3) does the article outline CAPO treatment recommendations for HIC settings or LMIC settings and, if so, is there a direct overlap with criteria #1; and 4) does the article identify any concerns or challenges with any of the treatment recommendations proposed for the management of CAPO? Disagreements regarding articles' eligibility were resolved by a third reviewer (PH), and literature deemed irrelevant to the topic of interest was excluded. The reference lists of included papers were also checked for relevant literature. Articles were excluded if full-text English was unavailable. Studies focusing on the pediatric population were excluded as this population is unique requiring specialised treatment and interventions above the scope of this study. Similarly, studies focusing on NCAPO

emergencies were excluded. Articles excluded were specific to ST-elevation myocardial infarctions (STEMI) and other cardiac abnormalities, in-hospital treatment, treatment focusing on the use of in-hospital devices to diagnosis CAPO, the use of devices requiring further training such as point of care ultrasound, and studies focusing specifically on extracorporeal membrane oxygenation (ECMO).

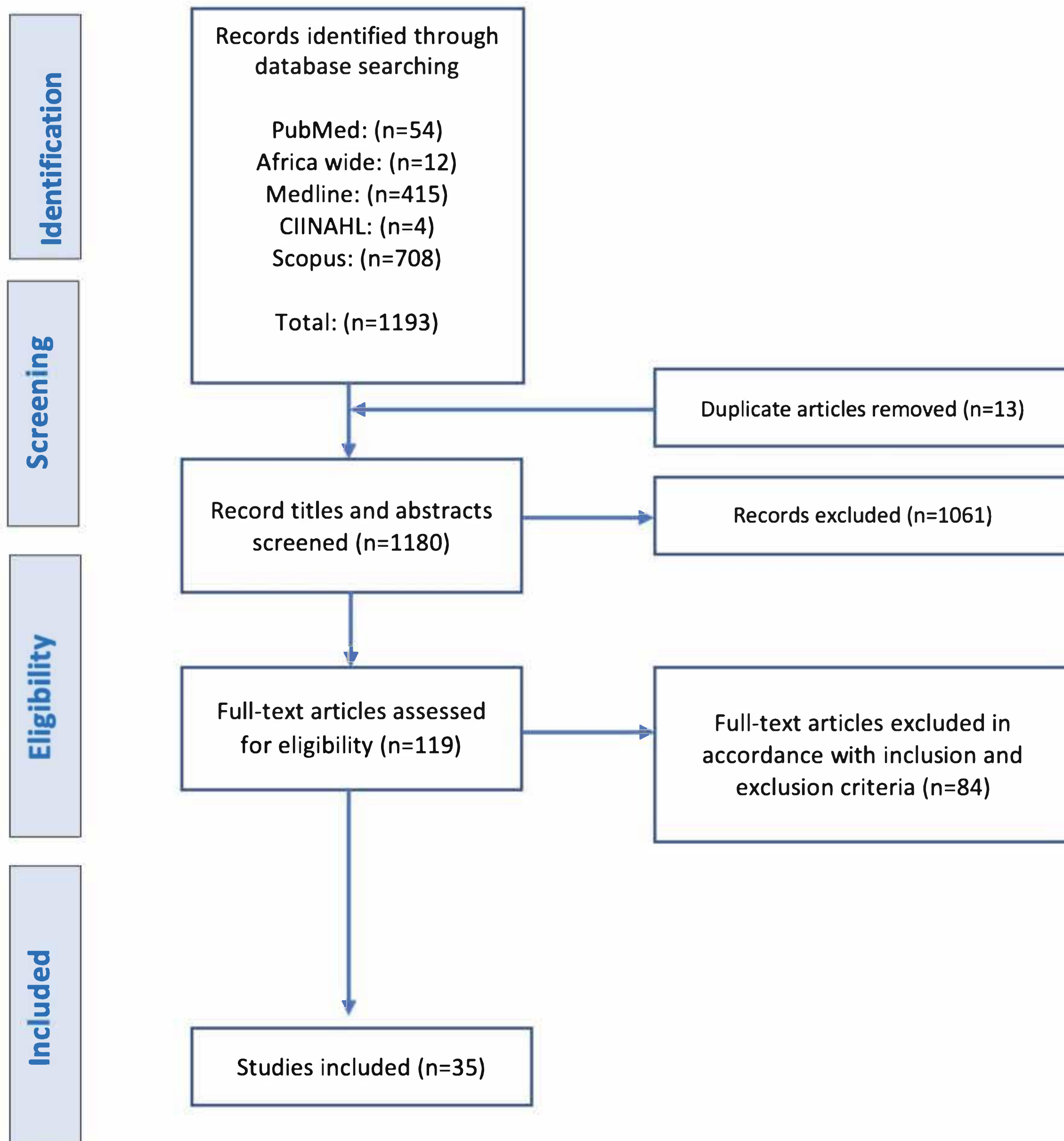

Figure 1: *PRISMA Flow chart for selected studies*

Data extraction and analysis

A data extraction table was developed in Microsoft Excel (RL, PH and CG). The extraction table provides a summary of research characteristics from the included articles, like the year of publication and setting, author(s), research design, aim, and primary outcome (Refer to Table 1).

After data extraction, the literature was analysed thematically by RL and verified by PH, JS, and CG. Results were reported descriptively, and the final included literature was not graded.

Results

Searches in all five databases identified 1193 articles, and 35 articles were included for the final review (Fig. 1). The 35 articles meeting the inclusion criteria presented prehospital AHF best practice recommendations, all from HIC contexts, including the United States of America (n=8), United Kingdom (n=2), Germany (n=3), Finland (n=2), Italy (n=3), France (n=5), Spain (n=3), Japan (n=1), the Netherlands (n=1), Canada (n=1), Denmark (n=1), Australia (n=1), Switzerland (n=1), and Scandinavia (n=1), and guidelines published in Europe (n=2). A total of thirteen (37%) articles were specific to the in-hospital setting (4, 8, 13, 14, 17, 18, 24, 28, 29, 32-35). Compared to thirty-five (100%) articles specific to the prehospital setting (1-35). There were no included articles specific to the LMIC context. (Table 1).

Of the 35 included studies, 34 (97%) articles addressed and provided guidance on the clinical presentation and prehospital diagnosis of AHF patients (1-15, 17-35). Thirty-four (97%) of the included articles provided insight into the best practice recommendations for the prehospital management of AHF patients (1-23, 25-35). Finally, 24 (69%) of the included articles addressed prehospital referral pathway considerations and priority areas

that may allow for optimal patient outcomes after experiencing an AHF episode (1-3, 5-9, 14, 16-18, 20, 22-23, 26-28, 30-35).

Nineteen (54%) of 35 articles identified current global CAPO clinical practice guidelines used in EMS systems (1-7, 13, 15, 17, 18, 20-23, 27, 28, 31, 33, 35). Twenty-one (60%) of the included articles identified potential challenges with CAPO guideline implementation in the prehospital setting (1, 2, 5-10, 13, 16-18, 20, 21, 23, 28-31, 33, 35). Twenty-five (71%) articles identified factors influencing the correct diagnosis of CAPO in the prehospital setting (1-3, 5-15, 17-21, 24, 26, 28, 31, 33, 35). A total of thirty (86%) articles discuss different challenges of CAPO practice guideline implementation and cost implications of different treatment strategies in the prehospital setting (1, 2, 4-7, 9-12, 14-19, 21-23, 25-25).

Facilitators and barriers relating to implementing CAPO clinical practice guidelines in the prehospital setting were identified. Eighteen (51%) articles identified facilitators to the use of the effective implementation of CAPO in the prehospital setting (4, 5, 9, 10, 12, 14, 15, 17, 18, 20, 21, 27-31, 33, 35). Furthermore, twenty-two (63%) articles were identified as potential barriers (1-4, 6, 7, 9-13, 15, 18, 20-22, 25-27, 31, 32, 35).

Discussion

To the best of the authors' knowledge, this is the first scoping review that addresses the context relevance of CAPO evidence-based recommendations for EMS settings in resource-limited settings. Overall, the authors did not find any published literature that holistically addressed prehospital diagnosis, management, and referral. As a result, three essential stages of care for the prehospital setting were identified as themes, namely, clinical presentation of CAPO and prehospital diagnosis; prehospital management and care; and referral pathways that facilitate better patient outcomes. These themes are discussed next.

Clinical presentation of CAPO and prehospital diagnosis

Emergency care providers' misdiagnosis of CAPO in the prehospital setting is multifaceted [27]. The clinical presentation of pulmonary oedema can be representative of various complex medical conditions, challenging the practitioner's ability to distinguish between CAPO versus non-CAPO as the cause. Additionally, the treating practitioner's educational level and subsequent scope of practice further influence their clinical decision-making of CAPO, which ultimately directs the selected course of treatment according to established clinical practice guidelines [40,41]. As a result, it is critical to accurately diagnosis CAPO [9,43].

However, the reviewed literature highlights that the prehospital diagnosis of CAPO is also heavily reliant on risk stratification and diagnostic tools often considered expensive to purchase and maintain in the resource-poor setting [44,45]. These diagnostic tools include, but are not limited to, ETCO2, arterial blood gases, ultrasound, invasive blood pressure monitoring and 12-lead ECGs [11]. All these tools require appropriate training and knowledge in their use. In the resource-limited prehospital setting, these diagnostic tools are often unavailable, or care providers' knowledge and training in their use may be limited. Additionally, prehospital risk stratification tools found within the literature are beneficial but often reliant on an assessment of biomarkers. Since risk stratification tools within the poorly resourced EMS setting have grown in use over the last few years, the development of a more context-appropriate CAPO risk stratification tool may be of benefit in these settings. Additionally, repeated physical examinations, echocardiography, and basic observations such as pulse rate characteristics, temperature gradients, urine output, skin mottling scores, three-lead ECGs, and blood pressure monitoring are typically available even in low-resource settings [11]. A diagnosis of CAPO in LMICs will likely depend on their use, and this area needs further investigation.

Risk stratification tools facilitate emergency care provider diagnosis, prognosis, and management of AHF

Shortening the time to appropriate treatment for AHF directly impacts mortality, morbidity, and overall hospital stay duration [43,46]. The reviewed literature highlighted that appropriate and timely patient-centred care and transportation could be facilitated using

risk stratification tools. In the context of AHF, risk stratification tools help distinguish the high-risk from the low-risk AHF patient [21,46,47,48]. This, in turn, also offers several benefits to resource-constrained healthcare settings. One such benefit involves availing valuable resources that can be better applied elsewhere in the healthcare system. This is because low-risk patients can be transported to less resource-intensive facilities, and scarce EMS critical care resources can be redirected to high-acuity prehospital assignments. Moreover, healthcare costs may be reduced for patients. Given the resource constraints in LMICs, such risk stratification tools can be essential in optimising the use of limited resources.

Most of the proposed AHF risk stratification tools rely on specific equipment that can potentially increase prehospital emergency care providers' diagnostic and prognostication capabilities [21,46,47,48]. Some of these resources include the use of biomarker point-of-care testing, ultrasounds, and invasive blood pressure monitoring [21,46,47,48]. Arguably, most of these resources are either unavailable or have not been well-researched for appropriateness in managing the AHF patient within the prehospital field. Moreover, some of these may not be cost-effective within resource-constrained EMS [6,7,11]. More studies need to be conducted focusing on the use of point-of-care testing in resource-constrained prehospital settings.

Prehospital management and care

Published literature lacked a standardised approach for the prehospital management of CAPO [49]. This is attributed to the different skill mixes found within prehospital settings. Most of the reviewed literature focuses on physician-led EMS, with a higher knowledge and skill set that facilitates decision-making and the management of CAPO patients.

Treatment principles of AHF according to best practice recommendations

The reviewed literature encourages the implementation of patient-centred treatment directives as an essential component for optimising overall patient outcomes [31,43,45]. These treatment goals are categorised into a) symptomatic relief, b) improved oxygenation, c) maintaining cardiac output, d) ensuring the perfusion of vital organs, and

e) reducing excess extracellular fluid accumulation [28,49,50]. Since CAPO is on the severe end of the clinical spectrum of AHF and is a major contributor to morbidity and mortality, much of the reviewed literature (97% n=34) addresses best practice recommendations for treating CAPO patients. However, some of the treatment recommendations for CAPO, although appropriate for HICs, might be questionable for use within resource-constrained EMS settings.

First, the early identification and intervention by non-invasive positive pressure ventilation (NIPPV) in patients with respiratory distress are beneficial. Specifically, the use of modalities such as continuous positive airway pressure (CPAP) in patients with respiratory distress has proven beneficial in reducing the need for intubation, invasive mechanical ventilation, and intensive care unit (ICU) stays [51,52,53,54,55]. Portable devices such as the disposable flow-safe CPAP mask has been shown to be equally effective as non-invasive mechanical ventilation (NIMV) at improving blood pressure, respiratory rate, and blood gas [53,56,57]. However, CPAP and similar NIPPV devices are expensive and still being adopted by many LMICs. In resource-constrained EMS settings, these devices may not be readily available [7,10,11]. In other instances where they are made available, the continuity of care might be challenging. Therefore, alternative positive pressure techniques that could be explored include the use of flow-safe and boussignac devices [55,56,58].

Second, the use of morphine was historically a standard practice in the treatment of CAPO due to its anxiolytic effects. However, due to the pathophysiology of CAPO and the general underlying hypotensive state of these patients, it is recommended to avoid its administration [22,31,32,59,60]. The published literature encourages the use of alternative agents such as Midazolam (benzodiazepines), which also offer benefits in avoiding the risk of hypotension [32]. In many LMICs, benzodiazepines are widely available since the World Health Organisation requires essential medicines as part of the standard medication in facilities. However, there is an unequal distribution of medication between urban and rural areas or public and private sectors in respective healthcare

settings, preventing optimal patient treatment and creating a further breakdown in continuity of care [61,62].

Finally, the use of nitrates CAPO's management has remained a controversial topic and lacks high-quality evidence to support practice [63,64,65,66,67]. Although nitrate administration may cause hypotension, the benefits have been shown to far outweigh the risks in the 'compensated, clinical normotensive' CAPO patient, and nitrates should thus not be withheld. Nitrates are also beneficial as the combination of actions at different dose ranges exponentially affects the smooth muscles. At low doses, it causes venodilatation resulting in a preload reduction. Conversely, increase dosages of nitrates result in the reduction of afterload and blood pressure because of its arteriolar dilatation effects [68,69,60]. However, nitrate administration should be guided by the continuous monitoring of 12-lead ECG, capnography, and blood pressure to reduce the risk of hypotension.

Interestingly, there is some controversy within the reviewed literature on the prehospital administration of nitrates, especially in the context of providing NIV/CPAP to the patient. In order to administer oral/sublingual nitrate, the clinician must break the seal during CPAP [70], and intravenous nitrate administration might be more fitting [63,64]. However, these interventions are not always readily available for use in resource-constrained settings and require intravenous medication devices. Alternatively, in resource-constrained EMS systems lacking CPAP/NIV capabilities, the early administration of oral/sublingual nitrates is beneficial in alleviating CAPO symptoms. In the case of decompensatory CAPO or cardiogenic shock, the priority is oxygenation and transportation to appropriate healthcare facilities, not requiring nitrate administration to reverse or avoid worsening symptoms of hypoxeamia [7,11].

Referral pathways that facilitate better patient outcomes

Acute referral pathway goals aim to ensure that patients receive the best treatment as timely and effortlessly as possible. The published literature highlighted that some patients did not rely on EMS for treatment and transfers to hospitals [72], but instead self-

presented to hospitals [72]. In other settings, patients self-presented to the closest general practitioner (GP) where appropriate resources were not in place to optimise care, and a referral via EMS was initiated by the GP [72]. These findings may either depict a referral pathway aimed at reducing the workload on EMS, perhaps promoting a more primary healthcare-aligned approach. As an alternative, it may also be representative of limited community awareness and a potential educational deficit of the services that EMS may render in their communities, or a potential distrust that the community may have of their EMS. The latter delays appropriate patient care.

While all of these factors highlight the current trends in patients' transportation to hospitals, there is no evidence of outcomes. However, within some of the reviewed literature, patients presenting to the emergency department by EMS seem to have had worse clinical presentations on arrival to the hospital than those patients who self-presented to the hospital [72]. In these instances, these patients first consulted a GP, where the GP called EMS for assistance [24,73]. The delay in appropriate care could be a contributing factor to the poor clinical presentation of such patients.

LMICs often have primary healthcare facilities and GPs but lack resources, community awareness, and education, while being burdened with unequal healthcare distribution, poverty, and inadequate governing policies. In such cases, EMS may have to take on the roles of the missing parts of the recommended referral pathway [10,74,75,76].

Appropriate referral pathways for AHF patients, especially in resource-constrained settings, are an area for future investigation, as this could offer several benefits to the patient and the healthcare system. Appropriate and context-relevant referral pathway systems are beneficial when implemented in healthcare systems. Referral pathways can reduce the financial burden on healthcare systems, reduce critical care prehospital emergency medical responses, and potentially avoid unnecessary hospitalisation for the low-risk AHF group [18,21,24,74,75].

Study limitations

According to the authors' knowledge, this is the first scoping review mapping the literature of CAPO diagnosis and treatment in the prehospital setting in LMIC. Study limitations may negatively influence the research outcomes and could limit present possible gaps in the current literature. Because of the nature of the scoping review, several limitations exist. Literature not published in English was excluded from the research; this could impact the different types of research possibly missing. A lack of published data regarding CAPO in LMIC in the prehospital is a limitation resulting in the contextualisation of data from CAPO in the prehospital HIC areas, relating toward bias of the English language.

The search was also limited to the timeframe January 2010–December 2022. The search timeframe limitation could result in the possibility of overlooking relevant data; however, an updated search was done in 2023 to review newly published research. Additionally, there is a possibility of overlooked relevant published and grey literature caused by specific search terms and limited access to databases. The data collection has the possibility of an unintentional limitation caused by selection bias as age, language, and demographics were used to guide included studies; to mitigate this, more than one researcher reviewed the results.

Furthermore, due to a lack of published literature specific to LMICs, contextualisation of the data was limited to direct experience.

Conclusion

CAPO is a severe subset of heart failure and should be treated as an emergency in the prehospital setting. Identifying CAPO can also be challenging, especially in the prehospital setting, where diagnostic devices, clinical practice guidelines, skill sets, and education vary compared to the in-hospital setting, especially in LMICs. Given the lack of existing literature, this review identified knowledge gaps, highlighting the need for further research in the prehospital setting in LMICs.

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Supplementary file

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

Table 1: Included articles for the scoping review

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
1	Mullen, R. 2013	Journal Paramedic Practice	Prehospital, United Kingdom	To discuss current practice guidelines and introduce the use of CPAP in ambulance services in the United Kingdom.	According to the authors, the introduction of CPAP in the prehospital setting in the UK is justified and feasible.	Barriers: Implementation of the use of CPAP in the UK - education, clinical expertise, financial constraints and lack of continuity of care
2	Bledsoe B.C. 2009	Occupational Risk	Prehospital, United States of America	To review current clinical practice guidelines of CAPO and AHF treatment in a case study.	The article reviews the importance of the early diagnosis and intervention of congestive heart failure and CAPO, specifying decompensatory congestive heart failure as an emergency. The use of morphine and diuretics should be	Barriers: Lack of continuity of care

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
					avoided as morphine results in the need for mechanical ventilators, longer hospital stays, admission to the ICU and mortality. Prehospital treatment should focus on the correction of hypoxemia and the administration of medication that improves cardiac output. The use of CPAP and nitrate administration for CAPO, and an ACE-inhibitor such as Enalapril as a second-line vasodilator, is recommended. The	

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
					authors encourage the use of benzodiazepines, such as Midazolam, Ativan, Versed, and Valium, as an anxiolytic. In the case of cardiogenic shock, the use of dobutamine or dopamine should be considered an inotrope.	
3	Fabre, M. et al. 2021	BMC Emergency Medicine	Prehospital, Geneva, Switzerland	To determine the association between prehospital hypercapnia and in-hospital units.	The study concluded there was an association between prehospital and in-hospital hypercapnia in patients with heart failure, causing a longer hospital stay.	Barriers: Different level of qualification, broader scope physician-led EMS.

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
4	Miró, Ò. et al. 2021	International Journal of Cardiology	In-hospital and Prehospital, Spain	To explore IV nitrates' effects on mortality, morbidity and adverse events when administered in prehospital and in-hospital settings.	The study analysed the impact of the prehospital use of intravenous (IV) nitroglycerin on patients in the emergency department. The authors concluded that using prehospital IV nitroglycerin was associated with a greater reduction of mortality and post-discharge events, compared to improvements in post-discharge events for patients receiving treatment in-hospital. The authors noted that	Facilitator: Patient-centered implementation of guidelines. Barrier: Broader scope physician-led EMS.

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
					further studies are required when assessing the early administration of IV nitroglycerin in the prehospital setting.	
5	Perlmutter, M.C. & Conterato, M. 2020	Prehospital and Disaster Medicine	Prehospital, Minnesota and Wisconsin, United States of America	To demonstrate the implementation of IV Bolus (IVB) NTG.	The study concluded that the administration of IVB is feasible and safe when administrated in the prehospital setting, with a noticeable reduction of blood pressure and improved oxygen saturation.	Facilitator: Compliance of guidelines Adverse Event: transient hypotension
6	Patrick, C. et al. 2020	Prehospital Emergency Care	Prehospital, Texas, United States of America	To assess the feasibility and safety of IVB nitrate	The main finding of the study reflected improvements in patients' symptoms on	Barrier: ○ Poor compliance of guidelines

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
				administration in the prehospital setting among patients with decompensatory CHF.	arrival at the hospital if they received IVB nitrate administration compared to their initial presentation before treatment. Transient hypotension was reported in one patient, and no intervention was required.	○ Poor differentiation for clinical diagnosis, Adverse Event: ○ transient hypotension ○ Undertreated, misdiagnosed
7	Harjola, P. et al. 2020	ESC Heart Failure	Prehospital, Spain	To evaluate prehospital management and protocols of AHF and CAPO by establishing the perceived difficulty of diagnosing AHF.	Diagnosing AHF and CAPO was easier than diagnosing a pulmonary embolism but more challenging than diagnosing an ST-segment myocardial infarction or asthma.	Barrier: ○ Lack of standardized paramedic education ○ Broader scope physician-led EMS. Adverse Event:

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
						Undertreated, misdiagnosed
8	Mancusi, C. et al. 2019	Echocardiography	In-hospital and Prehospital, Naples, Italy	To review the use of pocket-size ultrasound devices in the emergency department with patients presenting with undifferentiated dyspnoea.	The early use of pocket-sized handheld devices allows for prompt diagnosis and treatment of patients presenting with life-threatening conditions.	
9	Hensel, M. et al. 2019	American Journal of Emergency Medicine	Prehospital, Hamburg, Germany	To evaluate the efficacy of NIV in COPD and cardiogenic pulmonary oedema in the prehospital setting.	Even when transportation from the scene to the hospital is short, the use of NIV is beneficial among patients presenting with COPD and CPE. Early administration reduces	Facilitator: Compliance to guidelines Barriers: Physician-led, skill-mixed EMS.

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
					the length of hospital stay and the need for endotracheal intubation.	
10	Zanatta, M, et al. 2018	Critical Ultrasound Journal	Prehospital, Italy	To evaluate the efficacy and safety of prehospital ultrasound.	In patients presenting with CAPO and AHF, the use of ultrasound is both feasible and safe, although it has a rapid learning curve. It is also beneficial when used in the prehospital setting.	Facilitator: Differential diagnosis Barriers: Develop Ultrasound programs specifically for paramedic
11	Scharonow, M. & Weilbach, C. 2018	Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine	Prehospital, Scandinavia	To evaluate the use, efficacy, and quality of ultrasounds in the prehospital setting when diagnosing illnesses.	The prehospital use of the ultrasound was beneficial, and the findings correlated with the in-hospital diagnostic results.	Barrier: Ultrasound training for physician-led EMS

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
12	Harjola, P. et al. 2017	International Journal of Cardiology	Prehospital, Helsinki, Finland	To describe AHF patients self-presenting to the hospital and the prehospital treatment of patients with AHF.	Medication modalities to treat acute heart failure in the prehospital setting were low. Patients presenting by EMS had worse symptoms, heart rates and oxygen saturation than patients who self-presented. Patients presented with EMS had the greatest improvement on emergency department arrival. However, there was no difference in patients who both self-presented to hospital compared to those who presented by EMS.	Facilitator: ○ Compliance to guidelines ○ Patient severity EMS response Barrier: EMS skill-mix

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
13	Harjola, P. et al. 2017	European Journal of Heart Failure	In-hospital and prehospital, Helsinki, Finland	To describe the prehospital implementation and characteristics of patients who self-present with AHF to the emergency department.	The review concluded that patients with acute heart failure using EMS are rare, despite the condition's severity. The authors further concluded that a prospective clinical trial in this group could be challenging due to the limited group size.	Barriers: ○ Poor compliance of guidelines ○ EMS skill-mix ○ misdiagnosis
14	Laursen, C.B. et al. 2016	Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine	Prehospital, Odense, Denmark	To evaluate the prehospital treatment feasibility in patients with respiratory failure.	The use of prehospital lung ultrasound in a physician-based EMS sector is feasible and could be beneficial in ruling out CAPO in the prehospital setting.	Facilitator: Evidence of prehospital ultrasound efficiency Barrier: Physician-led, broader scope and expertise

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
15	Luiz, T. et al. 2016	In vivo (Athens, Greece) International Institute of Anticancer Research	Prehospital, Kaiserslautern, Germany	To demonstrate the use of CPAP in acute pulmonary oedema and decompensatory COPD cases in the prehospital setting in Germany.	The use of the Boussignac system as a CPAP delivery device for ACPE and COPD is safe and feasible in a physician-based EMS system.	Facilitator: ○ Compliance to guidelines ○ Prehospital use of alternative CPAP devices Barrier: Physician-led
16	Nieves, L.C. et al. 2015	Prehospital and Disaster Medicine	Prehospital, Colorado, United States of America	To assess the effects of high-dose furosemide administration.	High doses of furosemide administrated in the prehospital setting did not increase patients' length of hospital stay.	-
17	Mebazaa, A. et al. 2015	European Heart Journal	In-hospital and Prehospital, European	To review current recommendations and different experiences in	Risk stratification should include biomarkers and could indicate whether the	Facilitators: ○ Compliance of guidelines

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
				the prehospital and in-hospital setting with AHF patients.	treatment being administered is effective; however, further investigation is required.	○ Defining terminology ○ Specified resources and treatment in line with best practice
18	Pandor, A. et al. 2015	Health Technology Assessment	In-hospital and Prehospital, United Kingdom	To determine whether the use of prehospital NIV is more feasible ad effective compared to the current guidelines for patients presenting with acute respiratory failure.	The running costs to implement the use of CPAP in the prehospital setting are uncertain in the national health service (NHS). Evidence does not support prehospital BiPAP, so this method of NIV delivery would be ineffective.	Facilitators: Established need for CPAP. Barriers: ○ Challenge of practice gap ○ Feasibility ○ Education

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
19	Hunter, C.L. et al. 2015	Emergency Medicine Journal	Prehospital, Florida, United States of America	To assess prehospital end-tidal carbon dioxide (ETCO2) when differentiating between cardiac and non-cardiac causes of dyspnoea.	In the prehospital setting, lower levels of ETCO2 can be used to diagnose CHF dyspnoea.	-
20	Pan, A. et al. 2015	Emergency Medicine Journal	Prehospital, Ottawa, Canada	To determine the use and adverse effects of prehospital administration of furosemide.	No significant adverse event was found among patients who received higher doses of furosemide. Patients who received prehospital furosemide did not have a diagnosis of heart failure at hospital. No	Facilitators: Ability of paramedics compared to doctor to diagnose heart failure similar. Barrier: Misdiagnosis Adverse Event:

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
					definitive benefits were noted when administered in the prehospital setting.	Transient hypotension
21	Spijker, E.E. et al. 2013	International Journal of Emergency Medicine	Prehospital, The Haga hospital and The Hague, Netherlands	To evaluate the implementation, practical use and complications of CAPO in the prehospital setting.	Prehospital Boussignac CPAP (BCPAP) is safe and feasible based on a small sample size but requires further studies involving a larger sample size. A significant number of patients with CAPO in the prehospital setting are not treated according to protocols by using CPAP.	Facilitators: ○ Easy, feasible use of Boussignac CPAP mask ○ Nurses and physicians equally recognize CAPO. Barriers: Multi-professional EMS staff.

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
22	Bertini, P. et al. 2013	Prehospital Emergency Care	Prehospital, Livorno, Italy	To evaluate the effects of early treatment using short-acting beta-adrenergic antagonists in the prehospital setting in decompensatory CAPO using observational case series.	The early administration of beta-adrenergic antagonists (BAA) medications such as atenolol has been observed to have a positive effect by reducing dyspnoea and oxygen desaturation in the prehospital setting.	Barriers: ○ Poor compliance to guidelines ○ Physician-led EMS
23	Clemency, B.M. et al. 2013	Prehospital and Disaster Medicine	Prehospital, New York, United States of America	Determining the safety of multiple simultaneous nitroglycerin (MSN) tablets in patients presenting with heart failure in	The study concluded the use of multiple simultaneous nitroglycerin (MSN) tablets in patients presenting with heart failure in the prehospital setting is safe and	Adverse Event: Transient hyptension

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
				the prehospital setting.	hypotension is a rarer, self-limited event	
24	Oliver, C.M. et al. 2013	Journal of the Intensive Care Society	In-hospital and Prehospital, France	To demonstrate the use of early application of CPAP to reduce intubation, length of hospital stay, ICU admission in patients with hypercapnia and an impairment of left ventricular ejection fraction.	Early CPAP administration reduces patients' length of hospital stay compared to patients who were only treated with medications and not CPAP.	-
25	Templier, F. et al. 2012	American Journal of Emergency Medicine	Prehospital, France	To describe the use of prehospital NIV in compliance with CAPO national guidelines.	In French physician-based prehospital settings, the use of NIV modalities such as CPAP and pressure support ventilation	Barriers: Poor compliance to guidelines

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
					(PSV) complies with current recommendations for CAPO management but does not include other pathologies.	
26	Neesse, A. et al. 2012	European Journal of Emergency Medicine	Prehospital, Germany	To examine the feasibility and diagnostic accuracy of prehospital ultrasound for dyspnoea diagnosis using an algorithm.	The P-CHEST algorithm can be used to differentially diagnose dyspnoea in the prehospital setting. This is done by diagnosing the presence of a pleural effusion and is thought as being a novel marker to diagnose decompensatory CAPO and distinguished CAPO from COPD.	Barrier: ○ Physician-led EMS ○ Training programs specific for physicians.

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
					Further investigations are required.	
27	Dib, J.E. et al. 2012	Journal of Emergency Medicine	Prehospital, New Jersey, United States of America	To describe the prehospital use of CPAP in patients with acute severe heart failure.	The use of prehospital CPAP for CAPO is safe and effective as it improves haemodynamics, reducing the need for endotracheal intubation.	Facilitators: Compliance to guidelines Barriers: ○ Challenge of Paramedic education ○ Lack of standardization ○ Skills-mix of EMS
28	Ducros, L. et al. 2011	Intensive Care Medicine	In-hospital and Prehospital, France	To assess the safety, efficacy and benefits of using prehospital CPAP in CAPO.	The use of early CPAP in the prehospital setting is safe and effective with a continuation of care in the in-hospital setting.	Facilitators: ○ Compliance of guidelines ○ Risk stratification to minimize harm

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
						and improve patient outcome
29	Takahashi, M. et al. 2011	Journal of Cardiac Failure	In-hospital and Prehospital, Tokyo, Japan	To describe the relationship between time intervals of symptom onset in the prehospital setting to emergency room arrival.	Prehospital delays have a negative effect on Japanese patients presenting with CAPO and AHF. A reduction in prehospital delays would improve patient outcomes.	Facilitators: Well established evidence and implementation of guidelines.
30	Simpson, P.M., & Bendall, J.C. 2011	Emergency Medicine Journal	Prehospital, Australia	To describe the early use of NIV in the prehospital setting for patients with acute cardiogenic pulmonary oedema (ACPO),	Early administration of CPAP for CAPO improves CAPO symptoms and reduces the need for intubation.	Facilitators: ○ Context-fit guidelines ○ Compliance of guidelines

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
				determine the effects on mortality, the rate of intubations and length of hospital stay.		
31	Bates, K.D. 2010	EMS Magazine	Prehospital, United States of America	To identify practice guidelines for AHF and CAPO in the prehospital setting in the USA using case series.	Extrapolates early diagnosis, treatment, and appropriate disposition to hospital to continue care. The study also emphasized the probability of misdiagnosis in the prehospital setting and that examination should include differentiation from different emergencies.	Facilitators: Compliance of guidelines Barriers: ○ Misdiagnosis ○ Lack of standarisation

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
32	Miró, Ò. et al. 2021	European Heart Journal Acute Cardiovascular Care	In-hospital and Prehospital, Spain	To determine the effects of prehospital IV nitrates compared to in-hospital IV nitrates in AHF patients.	There is a reduction in mortality, morbidity and post-discharge events when IV nitrates are administered in the prehospital setting compared to post-discharge events when IV nitrates are administered in the in-hospital setting.	Barriers: Lack of standardisation
33	Mebazaa A. et al. 2016	Intensive Care Medicine	In-hospital and Prehospital, Paris, France	To describe the diagnosis and treatment of patients presenting with AHF and cardiogenic shock.	The early diagnosis, treatment, use of ultrasounds, NIV modalities, inotropes and mechanical ventilators for pressure support ventilation (PSV) are beneficial and safe.	Facilitators: Minimize harm, patient-centered algorithm.

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
34	Cluzol, L. et al. 2017	Archives of Cardiovascular Disease	In-hospital and Prehospital, Marseille, France	To describe treatment for AHF and CAPO.	Readmission and outcomes remain high irrespective of treatment and require both prehospital and in-hospital settings to work in synergy to improve AHF and CAPO readmission rates.	-
35	Beygui, F. et al. 2020	European Heart Journal Acute Cardiovascular Care	In-hospital and Prehospital, European	To provide symptom-based information with expert input specifically focused on the prehospital diagnosis and treatment of	Standardise practice guidelines are mandatory. Emergencies such as ST-segment myocardial infarction (STEMI) are well-established, while other cardiovascular diseases lack evidence and practice guidelines.	Facilitators: ○ Correct diagnosis challenging – based on clinical assessment, biomarkers and image findings

	Author(s), year	Journal	Setting	Aim	Main findings/outcome	Themes
				cardiovascular diseases.		○ Development of prehospital stratification Barriers: Lack of standardization

Abbreviation Key:

AHF - Acute Heart Failure; **BAA** - beta-adrenergic antagonists; **CPAP** - Continuous Positive Airway Pressure; **UK** - United Kingdom; **CAPO** - Cardiogenic Acute Pulmonary Oedema, **IV** - intravenous; **IVB** - intravenous bolus; **CHF**- Congestive Heart Failure; **NIV**- Non-Invasive Ventilation; **COPD** - Chronic Obstructive Pulmonary Disease; **EMS** - Emergency Medical Services; **NHS** - National Health Service; **ETCO2** - End-Tidal Carbon Dioxide; **BCPAP**- Boussignac Continuous Positive Airway Pressure; **ICU** - Intensive Care Unit; **PLUS** - Prehospital Lung Ultrasound

Part C: Appendices

Appendix A:

Relevant Journal Instruction to the Author(s)

The African Journal of Emergency Medicine (AFJEM) is the selected journal for publication as the authors believe that the study is relevant emergency care in low and middle-income countries.

Articles Instructions for authors(s) can be followed on these links:

http://www.afjem.com

http://cdn.elsevier.com/promis_misc/AfJEM-GFA.pdf

Mesh Terms

(TITLE-ABS-KEY (("emergency medical service*" OR prehospital OR "out of hospital" OR "first responder*"))) AND (TITLE-ABS-KEY (("practice guideline*" OR "clinical practice guideline*" OR management OR "treatment protocol*" OR "scope of practice" OR treatment*))) AND (TITLE-ABS-KEY (("heart failure" OR "flash pulmonary oedema" OR "flash pulmonary edema" OR "sympathetic crashing acute pulmonary edema" OR "sympathetic crashing acute pulmonary oedema" OR "pulmonary oedema" OR "pulmonary edema" OR "acute pulmonary oedema" OR apo OR "acute pulmonary edema" OR "cardiogenic pulmonary oedema" OR "cardiogenic pulmonary edema" OR "cardiogenic acute pulmonary edema" OR "cardiogenic acute pulmonary oedema")))

Appendix B: Research Protocol (as approved by Departmental Research Committee)

An investigation into the prehospital diagnosis, patient characteristics and treatment of cardiogenic Acute Pulmonary Oedema (APO) patients: A scoping review

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This proposal is submitted in partial fulfilment of the requirements for the degree Masters of Philosophy (MPHIL) Emergency Medicine Degree in the Faculty of Health Sciences at the University of Cape Town

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Declaration

I, Ruth Peggy Grace Lackay, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I authorise the University to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever. I further declare the following:

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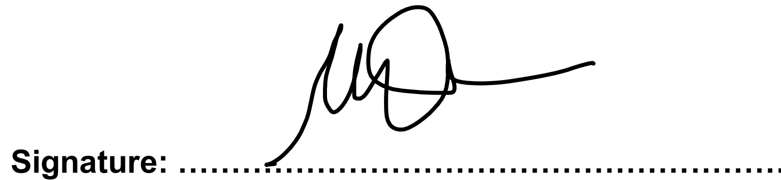

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Background

Acute Heart Failure (AHF) is a global emergency which has a high mortality and morbidity rate, after 60- to 90-day rehospitalization the risk of mortality increases from 25% to 30% because of factors involving cardiovascular and non-cardiovascular conditions.[1][2][3][4]

AHF is thought to be caused by an increase of cardiac filling pressures that leads to an increase of accumulation of fluid in both the pulmonary and alveolar spaces the increase of both the pressure and fluid accumulation lead to dyspnoea presenting with a subset of cardiac related illnesses such as Cardiogenic Acute Pulmonary Oedema (APO) and Sympathetic Crashing Acute Pulmonary O/Edema (SCAPE/O) or otherwise known as “flash pulmonary oedema” to name but a few. Moreover, as SCAPE/O is on the more severe spectrum of AHF early identification and treatment of these emergencies is pivotal to prevent the clinician from missing the narrow window to diagnose and manage the patient improving patient outcome.[5][6]

Historically, in the prehospital emergency care setting, patients who generally presented with cardiogenic APO were provided with standardized treatment consisting of high diuretics and morphine. However, recent evidence suggests that a dedicated clinical practise guideline (CPG) to guide prehospital providers on the management approach for patients presenting with cardiogenic APO were needed. Additionally, several concerns were raised including the routine use of high diuretic and opioid administration as standard care provided by emergency medical care personnel.[5] A growing body of evidence highlighted that the routine practise of high diuretic and opioid administration may be detrimental in certain subset of the disease, which include APO and SCAPE/O patients.[2][5] Furthermore, the change of practise also proposed that for SCAPE/O patients, no delay in initiating non-invasive ventilatory (NIV) support more specifically, continuous positive pressure airway pressure (CPAP) and nitrates (GTN), for the adult patient presenting with cardiogenic APO presenting to emergency medical services (EMS) in the prehospital setting.[7][8][9][10] The use of intravenous (IV) GTN can result in transient syncope and hypotension in patients in a decompensatory shock patient increasing the risk of mortality therefore GTN infusions should be administrated in an

adequate infusion devices to allow continuous and safe monitoring. Moreover, since the clinician only has a narrow window period to provide effective interventions to APO and SCAPE/O patients, it is imperative that the clinician is familiar with the clinical presentation of the illness and the appropriate management strategy that can be followed in the prehospital emergency care setting. Currently in some high-income countries (HIC) emergency medical services (EMS) settings have considered this best practice recommendation and have implemented a more structured management approach in the form of a CPG. This was implemented to not only promote patient safety, but also assist the clinician with appropriate management decision making about the best route of treatment after APO diagnosis. The CPG implementation have seen a decrease in mortality and morbidity rates of patients with APO. (6)(11)(12)

In 2018, the Health Professions Council of South Africa (HPCSA) updated its CPG for its EMS personnel advocating the use of NIV, CPAP, nitroglycerin (nitrates/GTN) spray of 0.4mcg per, for patients presenting with cardiogenic APO (only recently approved by the South African Health Products Regulatory Authority - SAHPRA). It is important to note that the change of CPG was based on international best practice recommendation, mostly from HIC setting, suggesting best treatment approach for cardiogenic APO patients in the prehospital setting. Most of these HIC healthcare systems, resources, demographics and infrastructure are different to that of South Africa, and other low-and-middle-income countries (LMIC) settings.(13)(14)(15)(16) However, fortunately other LMIC settings such as India, Turkey and Brazil have also advocated and adopted these best practice recommendations and implemented a dedicated cardiogenic APO CPG in emergencies centres. In these settings the change of guidelines have shown promising results as there were reports on positive patient improvement and reduction of ICU/hospital stay in many of these countries.(13)(14)(15)(16) Although these were positive outcomes in countries similar to that of South Africa, it is noted that South Africa, just like many other LMIC settings may still be limited in their ability to appropriately adopt these best practice recommendations accordingly due to several challenges which range from resource limitation, unequal distribution of resources, unequal wealthy status, and inequality of healthcare. (2)(17)(18)(19)(20)(21) Furthermore, the Western Cape is seen as one of the wealthiest provinces in South Africa, yet many parts within the province have an unequal

distribution of resources, with a documented increase of inequality since 2009. The unequal distribution of resources could be multifactorial, with the most prominent factors including previous apartheid segregation of specific communities, limited resource availability in areas, and the inequality of healthcare and resource allocation, causing an unavoidable challenge to instigate a dedicated CPG change requiring specific equipment. [16][22][23]

A scoping review (SCr) will be used to identify available literature on a structured management approach for treating cardiogenic APO in the prehospital setting. Furthermore, this scoping review will aim to identify any gaps in the literature that will assist future research endeavours in assisting with the development of a more structured, context fit, management approach for dedicated cardiogenic APO CPG in patients by EMS personnel working in the South Africa. In addition, the scoping review hopes to identify challenges in LMIC compared to HIC as resources are remarkedly different therefore discussing possible alternative management in LMIC countries as well as the cost implications for different treatment strategies. [24]

Research Aim

The aim of the scoping review is to examine the current evidence base surrounding the cardiogenic APO CPG that can be followed by EMS personnel.

Furthermore, the scoping review will aim to identify knowledge gaps in the literature that will assist future research endeavours to assist the development of a more structures, context fit, management approach for dedicated cardiogenic APO CPG in patients in the pre-hospital setting in South Africa.

Objectives

1. To Identify any cardiogenic APO CPG currently in use by EMS across the globe.
2. To Identify any challenges with the implementation of the cardiogenic APO CPG in the pre-hospital setting.

3. To identify any factors that influences the correct diagnosis of cardiogenic APO in the pre-hospital setting.
4. To identify different challenges in LMIC and HIC as well as discussing alternative management in LMIC countries and the cost implications of different treatment strategies in the pre-hospital setting.

Methodology

Study design

The research will form part of a qualitative approach by utilizing a scoping review. The SCr methodology will use the fundamentals of the Joanna Briggs Institute (JBI) when conducting SCr.[24] The principle of JBI builds on Arksey et al and Levacs et al framework when reviewing and describing literature.[25] Literature searches will be conducted to include search engines Pubmed, Medline, Embase, Cochrane, Web of Science and online CINAHL databases. In addition, any other literature known to the researcher or otherwise found in the reference list and deemed relevant to the aim of the scoping review and which were not identified in the database search. A combination of MESH terms will be identified but not limited to ((("Heart Failure"[Mesh] OR "Sympathetic Crashing Acute Pulmonary edema"[tw] OR "Cardiogenic acute pulmonary edema"[tw] OR "Flash pulmonary edema"[tw]) AND ("Emergency Medical Services"[Mesh] OR Prehospital* OR "Out of hospital"[tw] OR "Emergency Medical Servic*"[tw] OR "*first responder*"[tw])) AND ("Practice Guideline" [Publication Type] OR "Clinical Practice Guidelin*"[tw] OR Management[tw] OR "Treatment Protocol*"[tw] OR "scope of practice"[tw]))) Filters: from 2010 – 2021

After the search results are obtained from the electronic database search, the reviewer (RPGL) will scan the initial title and the abstract to identify relevant articles to the study. The priori inclusion and exclusion criteria will be used to ensure that all relevant articles are selected for the study. Furthermore, RPGL will review articles independently which has been selected ensuring rigor during the process by using the same priori inclusion

and exclusion criteria. In addition, both the selection process and selected articles will be reviewed therefore ensuring that the process is transparent and reproducible. [28]

Study setting and/or population

The research will use a SCr to answer the research question by specifically focussing on the prehospital setting. All relevant studies that meet the inclusion criteria listed will be considered for the review. Additionally, the use of a PRISMA SCr flow diagram (annexure 2) will be utilized to assist with the different phases in which information will flow through therefore mapping which articles will be included, excluded and the reasons why articles will be excluded as per the priori criteria. [29]

To help formulate a search strategy for this scoping review and to establish a priori inclusion and exclusion criteria, we will make use of the PCC method as described by Peters et al [1][25]

P (Participants) – Cardiogenic APO patients

C (Concept) – Clinical Practice Guidelines or Evidence based practice guidelines for management of cardiogenic APO patients by EMS personnel.

C (Context) – Prehospital emergency care setting and EMS personnel.

The inclusion criteria for the studies are the data range from January 2000 up to and including February 2021.

1. Cardiogenic APO Clinical Practice Guidelines or treatment recommendations for the prehospital setting
2. Cardiogenic APO Clinical Practice Guidelines or treatment recommendations for the emergency centre (medical)
3. Prehospital CPAP application recommendations for adults
4. Prehospital intravenous nitrates application recommendation for adults.
5. Adult patient population (18 years and older).

The exclusion criteria will be

1. Paediatric population treatment recommendations (define age group)
2. Published articles older than the year 2000

3. Non-English language research

Exclusion population

Paediatrics will be excluded from the study as this population underlying pathology or cause requiring interventions are more complex than the classified adult cardiogenic APO patient. Furthermore, the incident rate of pulmonary oedema occurring in this population is rare, one of the factors for this could be caused by the absence of coronary artery disease.(30)(31)

Recruitment and enrolment

The research makes use of a SCr and therefore will not include human subjects. An inclusion and exclusion criteria will be used to specify what information and data will be utilized for the study.

Research procedures and data collection methods

The study will not require WCG health approval as there will not be human participation.

A SCr is mainly used to give an overview of the existing evidence of information therefore the use of to assess the quality of methodology is not used. The methodological approach that will be used for the study will make use of a PRISMA SCr checklist. The aim of the PRISMA SCr checklist is to give guidance when reporting on the scoping review. Furthermore, the PRISMA SCr checklist will also assist with improving when reporting on SCr and inadvertently improving the relevance for decision making.

A search strategy will be used to further identify the information, the search strategy will formulate an inclusion and exclusion criteria. In doing so the researcher will be able to identify which articles to utilize.

Data analysis

The study will make use of a PRISMA SCr checklist as used by JBI. (27)(32)(33) (annexure 2) In addition, data charting will be utilized by collecting and reviewing studies (inclusion and exclusion criteria data), a second reviewer will cross-check studies that were added to the excel sheet that would have articles that have been included, excluded and requiring

a third reviewer for consensus. Regular meetings will be held between the reviewer RPGL and the supervisor to ensure trustworthiness of information by data analysis software (NVIVO version 12).[34]

Measurements and Results to be reported on

A database will be created using Microsoft excel spreadsheet where the following data from included studies will be recorded and analysed:

1. Year of study publication
2. Author(s) of the study
3. Study aim and objectives
4. Study setting
5. Study population
6. Study methodology
7. Patient clinical data if provided
8. Themes emerging

Data management

The search string from the study will be entered into a Microsoft Excel 2013 database. This database will be password secured and protected. The data will be saved in a shared folder between RPGL and Dr. Jared. A third reviewer will have access to the information if consensus is required. A further backup of the data will be saved onto a removable storage hard drive that RPGL will keep under lock and key. Access to the data on that drive will also be password secured and encrypted.

Trustworthiness

The use of two supervisors to review the data charting. Furthermore, the primary ethical concern will be the methodological and reporting quality of this scoping review. As a result, the researcher will make use of the PRISMA-SCr checklist, which has been formulated to facilitate complete and transparent reporting thereof. [27][32][33] [annexure 2]

Credibility

Purposive sampling will ensure credibility of the study. Furthermore, ensuring that the acceptable methodology will be adhered to throughout the study improves credibility. The

primary researcher will continue to build a good rapport with the supervisors ensuring continuous communication and transparency.[35]

Dependability

The research process will be reported in detail therefore enabling further or future research of the study. [35]

Transferability

The scoping review will allow for the primary researcher to describe the context thoroughly therefore the primary researcher hopes the contextual information, the methodology and the research information will allow the reader to be able to transfer the knowledge into their setting by contextualising implications the information will have on current practise. [35]

Confirmability

Neutrality will be achieved by unbiased opinions of the researcher and supervisors ensuring that two reviewers participate in the coding process therefore ensuring accountable of the team. Furthermore, continuous feedback, positive critique and reflective practises will help reduce researcher bias. [35]

Ethical considerations

There are minimal ethical considerations because:

1. There are no human or animal patients and /or participation in the study.
2. The study will not pose any direct risks or benefits to any persons as there will be no direct contact with participants.
3. No patient or participant information or data will be utilised in the study.
4. All data recorded will be entered into a password protected worksheet that is only accessible to RPGL and Dr Jared.
5. Data will be backed up to a shared folder on Dropbox only accessible to RL and Dr Jared, where access is protected by a password

6. A secondary back up will be made onto an external hard drive that is password protected and encrypted that will only be accessible to RPGL and kept under lock and key

Informed consent process

The study will focus on data resources collected by doing a scoping review and not use any form of participation that would require informed consent.

Privacy and confidentiality

After the information is collected it will be stored as SCr A on the researcher's laptop that is password protected. The information will also be backed-up to the University of Cape Town (UCT) One Drive. The researcher's laptop will be safely secured in a secure office at the residence.

Reimbursement for participation

There will not be participants therefore no remuneration will be paid from the study.

Strengths and limitations

The findings of this study will allow us to identify any gaps in the literature for the management of cardiogenic APO by pre-hospital providers, thereby guiding future research which is context fit.

The study has relevance to the South African context as cardiogenic APO is a high-risk medical emergency and a significant contributor to morbidity. South Africa has a diverse EMS landscape and currently lacks a structured cardiogenic APO management guide and the study hopes to contextualise implications for use in its EMS setting

The findings of this study may be beneficial for future cardiogenic APO patient management by pre-hospital staff in South Africa.

Dissemination of findings

Research finding will be made available in the form of a dissertation once data has been collected as per UCT guidelines.

Utilize the results from the study to assist with further motivation to develop and implement a dedicated prehospital cardiogenic APO CPG in South Africa.

Timeline

Main Activities	Date
EMDRC	January 2021
HREC (ethics)	February 2021
Data Search	February 2021
Data Analysis	April – May 2021
Write up	April – June 2021
Final Submission	July 2021

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26 April 2021

HREC/REF 268/2021

Prof P Hodkinson
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Dear Prof Hodkinson

PROJECT TITLE: AN INVESTIGATION INTO THE PREHOSPITAL DIAGNOSIS, PATIENT CHARACTERISTICS AND TRATMENT OF CARDIOGENIC ACUTE PULMONARY OEDEMA (APO)PATIENTS: A SCOPING REVIEW

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC note that the proposed study is a scoping review.

As the systematic review involves published literature available through publicly accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: "*Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research.*"

The HREC recommend that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to http://www.prisma-statement.org/.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015).

The HREC acknowledge that the MPHIL Candidate, Miss Ruth Lackay, is also involved in this project.

Yours sincerely

pp **PROFESSOR M BLOCKMAN**
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE