Update: Acute Heart Failure (II)

Pathogenesis and Clinical Presentation of Acute Heart Failure

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ABSTRACT

Acute heart failure constitutes a heterogeneous clinical syndrome, whose pathophysiology is complex and not completely understood. Given the diversity of clinical presentations, several different pathophysiological mechanisms along with factors triggering circulatory decompensation are involved. This article discusses the available evidence on the pathophysiological phenomena attributed or/and associated with episodes of acute heart failure and describes different clinical profiles, which, from a clinical perspective, constitute a key element for therapeutic decision-making.

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Patogenia y presentación clínica de la insuficiencia cardiaca aguda

RESUMEN

La insuficiencia cardiaca aguda es un síndrome clínico heterogéneo, cuya fisiopatología es compleja y no se conoce por completo. Dada la diversidad de formas de presentación clínica, intervienen en ella varios mecanismos fisiopatológicos diferentes, junto con factores que desencadenan una descompensación circulatoria. En este artículo se comenta la evidencia existente sobre los fenómenos fisiopatológicos atribuidos y/o asociados a los episodios de insuficiencia cardiaca aguda y se describen diferentes perfiles clínicos que, desde una perspectiva clínica, constituyen un elemento clave para la toma de decisiones terapéuticas.

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ACUTE HEART FAILURE: A COMPLEX CLINICAL SYNDROME WITH DISTINCT PATHOPHYSIOLOGIES

Acute heart failure (AHF) can be defined as a heterogeneous syndrome of signs and symptoms of new-onset or gradual/rapidly worsening heart failure (HF), requiring urgent therapy.[1,2] AHF constitutes a clinical syndrome with a complex and, more importantly, not completely understood pathophysiology.[3–5] Given the diversity of clinical presentations, several different pathophysiological mechanisms along with factors triggering circulatory decompensation are involved.[3–5] This article discusses the available evidence on pathophysiological phenomena attributed or/and associated with episodes of AHF

From the pathophysiological perspective, the a priori condition of AHF is heart dysfunction (including acute myocardial damage and remodeling) accompanied by dysfunction in systemic and pulmonary vasculature (with the involvement of endothelial dysfunction), which eventually lead to severe acute hemodynamic abnormalities. Their origin is not completely understood, but several generalized phenomena are postulated to be involved (neurohormonal activation, inflammatory process, oxidative stress). The contribution of dysfunction of other organs (kidneys, liver) is also suggested. Factors triggering AHF may include ischemia, hypertension, arrhythmias, noncardiac comorbidities, and administered drugs, etc.

NEUROHORMONAL ACTIVATION, INFLAMMATORY ACTIVATION AND OXIDATIVE STRESS

Circulatory decompensation is characterized by the presence of the following phenomena[3–5]: neurohormonal activation,[6–11] inflammatory activation,[12–14] and oxidative stress.[15–17] All these 3 entities, although obviously distinct, have several common features.

Firstly, they can be detected at the tissular level (within myocardial tissue and tissues of other affected organs, eg, kidneys), but also, due to their generalized nature, they may be tracked in peripheral circulation. Secondly, their role during hemodynamic stress is primarily adaptive, as they allow the increased effort performed by heart and circulatory system to be combatted, but only for a limited time. When they are preserved, they become maladaptive and detrimental, augmenting the circulatory

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insufficiency and impairing generalized homeostasis. Thirdly, they are involved in the progression of heart dysfunction, both during the acute phase of circulatory decompensation, and also afterwards, as their influence far exceeds beyond the episode of AHF and contributes to a steady progression of chronic HF. Finally, they are considered as strong predictors of poor outcome, being prognosticators of increased short- and long-term mortality as well as of an increased risk of recurrent hospitalizations due to subsequent episodes of AHF.

Neurohormonal activation includes the activation of the following systems and related signaling pathways: *a)* renin-angiotensin-aldosterone system[6]; *b)* sympathetic nervous system (with the depletion of the parasympathetic nervous system and associated abnormal cardiopulmonary reflex control, ie, attenuated baroreflex, augmented central and peripheral chemoreflexes)[7]; *c)* arginine vasopressin (along with copeptin, the C-terminal segment of pre-pro-vasopressin as a stable and reliable surrogate for vasopressin)[8]; *d)* endothelin-1[9]; *e)* adrenomedullin,[10] and *f)* the system of natriuretic peptides.[11]

Inflammatory reaction includes predominantly an activation of innate immune response, an increased expression of proinflammatory mediators (such us tumor necrosis factor, interleukin-1, interleukin-6, ST-2), activation of the complement system, autoantibody production, and overexpression of major histocompatibility complex molecules as well as adhesion molecules.[12–14]

Oxidative stress is associated with an excess of reactive oxygen species, which, for example, react with nitric oxide, disrupt physiologic signaling, and lead to the production of toxic and reactive molecules (peroxynitrite, isoprostane, aminothiols), and increased purine catabolism, which in turn increases xanthine oxidase activity and subsequently serum uric acid levels and also induces an augmented release of myeloperoxidase by activated neutrophils and monocytes.[15–17]

Most importantly, all these aforementioned pathomechanisms are the primary mechanisms of a proven role in the progression of HF predominantly in its chronic/stable phase. They have been demonstrated during episodes of AHF in observational/descriptive studies but there is no major mechanistic proof in acute settings.

MYOCARDIAL DYSFUNCTION

Circulatory decompensation always occurs in patients with abnormal function of the myocardium, but heart dysfunction demonstrated in patients with AHF varies in its character (systolic/diastolic dysfunction, left/right heart), triggering factor (ischemia, inflammation, hypertension) and clinical course (rapid, gradual worsening), etc.[4,5,18] Systolic function of the left ventricle may vary from normal to severely impaired and be accompanied by diastolic dysfunction or mitral regurgitation. An important clinical problem is right ventricular dysfunction, which usually complicates the dysfunction of the left heart. All these abnormalities affect the symptoms of AHF are associated with unfavorable clinical outcomes.[3,4,18]

Abnormalities seen within the myocardium during AHF are most likely due to the afore-mentioned phenomena: *a)* neurohormonal activation; *b)* inflammatory activation, and *c)* oxidative stress. They are related to progressed myocardial dysfunction and associated structural abnormalities, including cardiomyocyte hypertrophy, cardiomyocyte apoptosis, depressed myocardial contractility, inhibited cardiomyocyte responsiveness to β-adrenergic stimulation, fibroblast growth, fibrosis, and remodeling, to name but a few.

Regardless of the underlying molecular mechanisms and triggering factors, episodes of AHF are postulated to be associated with marked cardiomyocyte loss (necrosis) and dynamic changes in the architecture of the myocardial extracellular matrix (remodeling). Cardiomyocyte damage can be reflected by confirmation of high levels of circulating cardiac troponins.[19] For example, in the ADHERE registry, detectable cardiac troponins were confirmed in 75% of patients hospitalized due to AHF, and carried poor prognosis.[20] The triggering/acceleration of myocardial remodeling during AHF may be reflected by an increased expression of molecules belonging to 2 groups of molecules involved in the regulation of the dynamically changing status of extracellular matrix, ie, matrix metalloproteinases (MMPs) degrading fibrillar collagens and tissue inhibitors of metalloproteinases (TIMPs),[21] as well as galectin 3, a β-galactoside–binding lectin produced mainly by macrophages, involved in the fibroblast activation and tissue fibrosis.[22]

ENDOTHELIAL DYSFUNCTION

Acute heart failure is also characterized by generalized endothelial dysfunction (some authors call this pathology endothelitis). This dysfunction may be due to an imbalance within neurohormonal, inflammatory and oxidative milieu in the circulation and endothelial cells, as well as due to other unidentified factors, which clinically may cause: *a)* myocardial hypoperfusion, reduced coronary flow and ischemic dysfunction; *b)* increased vascular stiffness and impaired arterial distensibility further aggravating myocardial damage; *c)* vasoconstriction within the systemic and pulmonary circulation, resulting in an increased left and right ventricular afterload; *d)* endothelin-related secondary increased sympathetic drive and catecholamine release, and *e)* renal dysfunction, reflected mainly by the reduced sodium excretion, but also associated with other abnormalities.[23]

OTHER ORGAN DYSFUNCTION (KIDNEYS, LIVER)

Importantly, heart dysfunction itself is only one element of the complex pathophysiology of AHF, and other abnormalities within vasculature and peripheral pathomechanisms involving other body organs (eg, kidneys, liver, endothelium, lungs) play a critical (if not always dominant) role.[3–5,24,25]

Renal dysfunction plays an important role in the pathophysiology of AHF, but its origin is not completely understood. In addition, the pathophysiology of the contribution of renal dysfunction as a factor aggravating or triggering an episode of AHF, as well as contributing to the further progression of HF and poor outcomes, remains unclear.[3,4,25,26]

Renal dysfunction includes decreased glomerular filtration rate (assessed using different glomerular filtration rate [GFR] formulas based on the measurement of circulating creatinine, cystatin C), abnormal tubular function (reflected by high levels of neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule 1 [KIM1] in both peripheral blood and urine) and inadequate

endocrine activity (inadequate secretion of erythropoietin [EPO], renin). It is suggested that renal dysfunction may be due to generalized neurohormonal activation, inflammation, oxidative stress, impaired intrarenal hemodynamics as a consequence of either abnormal extrarenal hemodynamics affecting renal blood flow and pressures or deranged intrarenal haemodynamic regulatory mechanisms, intrinsic renal disease (eg, diabetes, hypertension), and iatrogenic causes (eg, high-dose loop diuretic therapy).[3,4,25–28]

HEMODYNAMIC RESPONSE

Acute heart failure is associated with a wide range of abnormal hemodynamic responses, which include typically reduced cardiac output, increased filling pressures, and augmented afterload.[1,2]

The pathomechanisms directly leading to circulatory decompensation are not completely clear. Although pulmonary or/and peripheral congestion remain a prominent feature of AHF,[1–5] importantly only approximately 50% of patients develop a significant increase in body weight associated with real fluid accumulation.[29] Currently, there are 2 concepts, in which the underlying pathomechanisms of congestions are diverse, ie, exogenous fluid acumination is confronted with endogenous fluid shift from venous body reservoirs.[30–32]

The first theory is more conventional and based on the assumption that congestion is due to sodium and water retention, which occurs gradually (days, weeks) and is associated with exogenous fluid accumulation, increased body weight, increased effective circulatory volume, and prominent renal dysfunction.[1,2,32]

The second theory has been recently proposed and is based on the hypothesis that congestion is the consequence of endogenous fluid shift, which occurs rapidly (hours) and is associated mainly with an increase in sympathetic outflow causing vasoconstriction in venous capacitance vessels and leading to a shift of volume from venous blood reservoir (probably mainly from the splanchnic reservoir) into the systemic circulation. It is not associated with an accumulation of additional exogenous fluid or with body weight gain.[30–32]

The latter mechanism belongs to a conservative adaptive mechanisms, acting against orthostasis and providing an additional preload circulatory volume in response to standing, exercise, stress, and trauma.[30–32] In healthy individuals, this reflex mechanism is beneficial and does not cause an increase of filling pressures and related congestion. In patients with HF with abnormal pressure-volume loops, even a relatively small sympathetically-mediated shift of volume may inadequately increase pulmonary pressures and lead to fluid extravasation and congestion.[30–32] The factors triggering a relative acute sympathetic activation may be different. According to some authors, an augmented tonic and episodic activity of chemoreceptors (mainly peripheral), without an evident water and natrium accumulation, may be attributable to rapid episodes of AHF.[30]

MULTIPLE CLINICAL PRESENTATIONS – A TYPICAL FEATURE OF ACUTE HEART FAILURE

Because AHF may comprise a wide spectrum of clinical conditions with different underlying pathophysiologies and precipitating factors, a patient admitted to hospital for AHF may have a variety of clinical manifestations. Additionally, during hospital stay, clinical conditions may dynamically change with resultant changes in signs, symptoms, and clinical presentations. Thus, careful and comprehensive evaluation of each patient with AHF at each stage of in-hospital management is fundamental to adjust therapy to actual clinical conditions.

Clinical Diagnosis of Acute Heart Failure

The initial diagnosis of AHF is based on the presence of clinical symptoms and signs and is further confirmed by appropriate additional investigations such as ECG, chest X-ray, laboratory assessment (with specific biomarkers), and echocardiography.[1,2]

Typically, the clinical picture reflects fluid retention (pulmonary congestion and/or peripheral edema) and is less often related to reduced cardiac output with peripheral hypoperfusion.[1–4]

Symptoms of AHF are manifestation of congestion, reflecting elevated ventricular filling pressures; left-sided may be characterized by orthopnea, paroxysmal nocturnal dyspnea, and breathlessness at rest or with minimal exertion, whereas right-sided can be characterized by peripheral edema, ascites, and symptoms of gut congestion. Systematic physical examination is essential in the diagnostic process of AHF and should always contain an evaluation of the following:

- Peripheral perfusion, for which low systolic blood pressure and cold skin temperature are the most accessible measures of hypoperfusion; additionally, the patient may show confusion, dizziness, and anuria/oliguria.
- The presence of signs associated with elevated filling-pressures (left-sided: bi-basal rales, an audible third heart sound, an abnormal blood pressure response to the Valsalva maneuver, or right-sided: elevated jugular venous distention, hepatojugular reflux, hepatomegaly, ascites, and peripheral edema; pleural effusions are often seen in patients with a previous history of chronic HF).

The sensitivity and specificity of symptoms and signs to predict both clinical scenarios, ie, elevated filling pressures or low cardiac output is often unsatisfactory,[33] which leaves a relatively large margin of uncertainty to confirm the final diagnosis of AHF and initiate appropriate treatment. Thus, in the diagnostic algorithm, careful clinical evaluation should be followed by additional investigations.[1,2]

Notably, the severity of initial signs and symptoms does not always correlate with outcomes. As an illustrative example, a patient who presents with elevated blood pressure and severe respiratory distress with pulmonary edema may have better prognosis than a patient with chronic heart failure and low left ventricular ejection fraction (LVEF), who develops gradual deterioration and shows peripheral edema, rales, and low blood pressure.

Clinical Classifications: View From the Recent Guidelines

According to the European Society of Cardiology guidelines,[1] a patient with AHF may present with one of the following clinical categories:

Decompensated Chronic Heart Failure

When a patient with chronic HF develops progressive deterioration and worsening in signs and symptoms; peripheral edema and/or pulmonary congestion are characteristic for this clinical

category; these patients may appear with low blood pressure which is often associated with impaired LVEF and predicts poor prognosis.

Pulmonary Edema

For many physicians, pulmonary edema is the real clinical presentation of AHF; typically, signs and symptoms develop rapidly and patients demonstrate severe respiratory distress with tachypnea, orthopnea, and pulmonary congestion.

Hypertensive Heart Failure

Hypertensive heart failure is associated with elevated blood pressure with accompanying dyspnea and signs of pulmonary congestion, often in patients with relatively preserved LVEF.

Isolated Right Heart Failure

Isolated right heart failure is characterized by low output syndrome in the absence of pulmonary congestion, with low left ventricle filling pressures; importantly, a clear differentiation is needed here between patients with chronic HF who gradually develop signs and symptoms of right HF (elevated jugular venous pressure, peripheral edema, hepatomegaly, gut congestion), which at some stage dominate the clinical picture vs patients with new-onset isolated right heart failure, often secondary to either acute coronary syndrome (ACS) or pulmonary embolism; although the former does not fulfil the diagnostic criteria–often with some pulmonary congestion and elevated left ventricular filling pressure–, many physicians tend to put such patients into this category.

Cardiogenic Shock

Cardiogenic shock characterizes severe peripheral hypoperfusion with subsequent end-organs damage; typically it is associated with low blood pressure (systolic BP < 90 mmHg) and low urine output (< 0.5 mL/kg/min).

Acute Coronary Syndrome Complicated by Heart Failure

Up to 15% to 20% of patients admitted with ACS have signs and symptoms of heart failure and an additional 10% develop HF during hospital stay[34]; the incidence is even higher in reports focusing on patients with a diagnosis of AHF, where up to 40% may have ACS as a precipitating factor[35]; interestingly, ACS complicated by AHF is now often viewed as a separate clinical entity, characterized by complex structural, hemodynamic and neurohormonal interactions, the need for urgent referral for coronary intervention, and poor outcome; on the other hand, patients with AHF often demonstrate troponin release (typically of moderate magnitude)[19,20] which may further complicate the whole diagnostic process.

Recent AHA/ACC guidelines tend to indicate a lack of widely-accepted nomenclature for HF syndromes requiring hospitalization[2] and instead of "the AHF patient" propose "the hospitalized HF patient" with the following subgroup classification: *a)* patients with acute coronary ischemia; *b)* patients with accelerated hypertension with acutely decompensated HF; *c)* patients with shock; *d)* patients with acutely worsening right HF; and *e)* patients with decompensation after surgical procedures.

The differentiation of patients with AHF complicating surgical procedures in a separate clinical entity is an interesting approach. This category was previously proposed by Gheroghiade and Pang[4] as occurring in patients with or without previous ventricular dysfunction, often related to worsening diastolic function and volume overload immediately after surgery and the subsequent early postoperative period. It can be also caused by cardiac injury related to surgical procedures.[4]

Importantly, these classifications, although they characterize important underlying pathophysiological and clinical features with precipitating factors, may not have a direct translation into therapeutic decisions in routine clinical practice.

Clinical Profiling: Key for Therapeutic Decisions in Acute Heart Failure

Acute HF comprises a wide spectrum of clinical conditions ranging from gradual worsening of chronic conditions (ie, peripheral edema and dyspnea) to pulmonary edema or cardiogenic shock. For clinical purposes, characterizing the patient's clinical profile at each phase of AHF management constitutes a key element for therapeutic decision-making.

On admission, in parallel with the diagnostic process to confirm AHF, careful evaluation of clinical status to identify the clinical profile characterizing life-threatening conditions is obligatory.[1] In this context, the following clinical profiles may be present:

- Respiratory failure with inadequate ventilation and peripheral oxygenation; in such cases, oxygen should be administered; in more severe cases, there may be a need for endotracheal intubation and invasive ventilation.
- Presence of life-threatening tachy- or bradyarrhythmias with a need for urgent electrical cardioversion or temporary pacing.
- Peripheral hypoperfusion (typically with low systolic blood pressure, sometimes with a clinical picture of cardiogenic shock); often there is a need for inotropic agents, vasopressors or, in most severe cases, mechanical circulatory support.
- Hemodynamic deterioration due to acute mechanical cause (eg, acute interventricular septal or mitral valve papillary rupture in ACS, acute valvular incompetence due to endocarditis).
- Acute coronary syndrome as an underlying cause for decompensation with urgent transfer to a catheterization laboratory with subsequent coronary reperfusion.

As the AHF pathophysiology is a consequence of elevated ventricular filling pressure and reduced cardiac output, hemodynamic profiling of a patient is often used in clinical practice. Typically, it is based on bedside evaluation of congestion and perfusion,[32,36] which allows differentiation of 4 different "hemodynamic" profiles[37]:

- "Wet and warm". Most commonly present with patients demonstrating congestion (wet profile) and still adequate peripheral perfusion (warm profile).
- "Wet and cold". With congestion and inadequate peripheral perfusion (cold profile).
- "Dry and cold". With impaired perfusion and lack of congestion.
- "Dry and warm". Often with symptoms of AHF, but rather compromised hemodynamics.

Hemodynamic profiles are associated with outcome (patients with "wet and cold" characteristic having the worst prognosis)[36]

but more importantly they may also have important therapeutic implications.

Acute Heart Failure Patient With Congestion: Fluid Accumulation or Redistribution?

Signs and symptoms of fluid overload are present in most patients hospitalized due to HF decompensation, whereas only a minority demonstrate significantly impaired peripheral perfusion and hypotension.[30–32,36] This explains why the "wet and warm" profile (depicting congestion with adequate peripheral perfusion) is most commonly seen in these clinical settings. However, the "warm and wet" profile may comprise 2 groups of patients with different clinical characteristics and pathophysiological profiles[32,38]:

- "*Cardiac*" *Profile*. This profile typically occurs in patients with a history of chronic HF, impaired LVEF, slow symptomatic deterioration, gradual (over several days-weeks) fluid accumulation with concomitant weight gain and dominating signs of peripheral edema, jugular venous distension, and hepatomegaly; some of these patients may also present low systolic blood pressure.
- "*Vascular*" *Profile*. This profile is characterized as rapid clinical deterioration (typically within hours), with severe dyspnea, evidence of pulmonary congestion (in the most severe cases in a form of pulmonary edema), with no (or only minimal) weight gain, where fluid redistribution to the lungs is essential for symptoms; these patients often have preserved LVEF and present with normal or elevated systolic blood pressure.

The former profile occurs due to sodium and water retention with resultant body fluid overload, whereas the latter is often seen in patients with no evidence of fluid retention, and vasoconstriction may play a dominant role. This explains the background for different treatment strategies often applied for these clinical profiles: diuretics for those with the "cardiac" profile and a combination of vasoactive agents with diuretics for those with the "vascular" profile.

In-hospital Heart Failure Worsening: A Newly Recognized Clinical Profile

The natural course of AHF can comprise a clinical scenario characterized by initial stabilization with symptomatic improvement, followed by often sudden and unexpected deterioration, worsening of symptoms and signs of AHF, requiring intensification of therapy. This clinical profile has only recently been recognized as worsening heart failure (WHF), which is associated with adverse outcomes[39,40] and may constitute potential a therapeutic target in AHF.[41] Between 10% and 30% of AHF patients may develop WHF during hospital stay. WHF always represents a meanigful change in clinical status, with variable clinical manifestations (from only symptomatic deterioration to severe hemodynamic collapse with peripheral hyporefusion). However, is has not been yet established whether it is a distinct entity or is rather an indicator of more severe disease at the time of admission. There is growing evidence that it may be associated with the markers of end-organ damage with further ominous consequences for long-term prognosis. In this context, it remains unanswered whether the development of this injurious profile can be predicted and subsequently prevented. Interestingly, in the RELAX-AHF study, treatment with serelaxin was associated with a 30% reduction in WHF at day 14[42] whereas rolophylline, which enhances diuresis, failed to prevent WHF

in the PROTECT study.[43] Additionally, it is not known whether the prevention of WHF can have a favorable effect on longer-term adverse outcomes. Despite all these uncertainties, the clinical profile of WHF needs to be recognized in everyday practice and should always be considerd and in high-risk patients.

Clinical Profile and Comorbidities

The clinical presentation of an individual patient admitted with AHF is often influenced by distinct characteristics of cardiovascular and noncardiovascular comorbidities. The prevalence of comorbidities among patients admitted due to AHF is very high. Recent data from the ESC HF Registry demonstrate that atrial fibrillation is present in 44% of AHF patients, diabetes mellitus in 39%, chronic obstructive pulmonary disease in 20%, and renal dysfunction in 26%.[44] Our study showed that only 25% admitted with AHF tended to have preserved iron status, whereas the remaining 75% had laboratory indices characterizing either depleted body iron stores or insufficient iron uptake by metabolizing cells.[45] This shows that iron deficiency (irrespectively of the presence of anaemia) often coincides with HF decompensation.

In the process of profiling AHF patients, a history of concomitant disorders carries an important practical message as the presence of comorbidities may interact with diagnosis, treatment, and the outcomes. For example, in patients with chronic obstructive pulmonary disease, the underlying cause of dyspnea (either cardiac or pulmonary), either on admission or during hospital stay, is often difficult to establish and regular assessment of natriuretic peptides may be helpful. A certain degree of renal function impairment is present in most AHF patients who are referred as cardio-renal syndrome type I (ie, abrupt worsening of cardiac function leads to acute kidney injury). As already discussed, impaired hemodynamics (decreased cardiac output and increased venous pressure) together with neurohormonal activation and concomitant pharmacological therapy (mainly excessive use of diuretics) are major pathophysiological determinants.[1,2] Evaluation of renal function (with a diagnosis of cardio-renal syndrome) should be considered as an integral element in the clinical profiling of AHF patients at each stage of in-hospital management, as this information has therapeutic and prognostic implications.

The unsatisfactory results of most recently completed large clinical trials in patients with acute HF[46–48] clearly suggest a need for change in the traditional paradigm of diagnosis and treatment in this complex clinical syndrome. In the context of underlying pathophysiological mechanisms, we need to see AHF as a multifaceted, heterogonous clinical syndrome with different, often not clearly understood pathophysiologies. In the context of clinical presentation, a patient admitted with AHF may show a wide spectrum of clinical profiles, typically related to cardiovascular status before decompensation, precipitating factors, and cardiovascular and noncardiovascular comorbidities. Profiling patients at each stage of in-hospital management allows the identification of the high-risk population (including those with life-threatening conditions) and is essential for a targeted approach to optimize AHF treatment.

CONFLICTS OF INTEREST

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