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ORIGINAL ARTICLE

Prediction of cardiac worsening through to cardiogenic shock in patients with acute heart failure

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Abstract

Aims Acute heart failure (AHF) can result in worsening of heart failure (WHF), cardiogenic shock (CS), or death. Risk factors for these adverse outcomes are not well characterized. This study aimed to identify predictors for WHF or new-onset CS in patients hospitalized for AHF.

Methods and results Prospective cohort study enrolling consecutive patients with AHF admitted to a large tertiary care centre with follow-up until death or discharge. WHF was defined by the RELAX-AHF-2 criteria. CS was defined as SCAI stages B–E. Potential predictors were assessed by fitting logistic regression models adjusted for age and sex. *N* = 233 patients were enrolled, median age was 78 years, and 80 were women (35.9%). Ischaemic cardiomyopathy was present in 82 patients (40.8%). Overall, 96 (44.2%) developed WHF and 18 (9.7%) CS. In-hospital death (8/223, 3.6%) was related to both events (WHF: OR 6.64, 95% CI 1.21–36.55, $P = 0.03$; CS: OR 38.27, 95% CI 6.32–231.81, $P < 0.001$). Chronic kidney disease (OR 2.20, 95% CI 1.25–3.93, $P = 0.007$), logarithmized serum creatinine (OR 2.90, 95% CI 1.51–5.82, $P = 0.002$), cystatin c (OR 1.86, 95% CI 1.27–2.77, $P = 0.002$), tricuspid valve regurgitation (OR 2.08, 95% CI 1.11–3.94, $P = 0.023$) and logarithmized pro-adrenomedullin (OR 3.01, 95% CI 1.75–5.38, $P < 0.001$) were significant predictors of WHF. Chronic kidney disease (OR 3.17, 95% CI 1.16–9.58, $P = 0.03$), cystatin c (OR 1.88, 95% CI 1.00–3.53, $P = 0.045$), logarithmized pro-adrenomedullin (OR 2.90, 95% CI 1.19–7.19, $P = 0.019$), and tricuspid valve regurgitation (OR 10.44, 95% CI 2.61–70.00, $P = 0.003$) were significantly with new-onset CS.

Conclusions Half of patients admitted with AHF experience WHF or new-onset CS. Chronic kidney disease, tricuspid valve regurgitation, and elevated pro-adrenomedullin concentrations predict these events. They could potentially serve as early warning signs for further deterioration in AHF patients.

Keywords Acute heart failure; Cardiogenic shock; Prediction; Pro-adrenomedullin; Risk; Worsening heart failure

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Introduction

Acute heart failure (AHF) describes an acute presentation to hospital with signs and symptoms of heart failure. AHF can be the first presentation of previously undiagnosed heart failure or due to worsening pre-existing heart failure.[1] AHF is a frequent cause for emergency unit visits and hospitalization in general; in the elderly as well as in heart failure patients it is even the main cause of hospitalization.[2]

Patients with AHF have poor outcomes: Approximately 4–10% of patients die during their hospital stay[3,4]; 1-year mortality varies between 20 and 36%.[3] Thus, hospitalization due to AHF is a landmark event in the disease's trajectory and highlights a vulnerable phase which continues after discharge. AHF has therefore been described as a signal identifying patients in need of additional care and attention.[2,5,6]

Worsening heart failure (WHF) has been identified as a marker of exceed risk in AHF patients previously.[7] It is associated with longer hospital stays and mortality.[8,9] There is no universal definition, leading to slightly varying criteria in clinical trials.[7] Key aspects like treatment escalation (starting or increasing vasopressors, initiation of renal re-

placement therapy or mechanical circulatory support) are largely included, for example, by the RELAX-AHF-2 trial.[10] WHF occurs in 7–42% of all patients hospitalized for AHF, vastly depending on the precise criteria and the time of censoring.[8,10–14]

Some AHF patients present with or progress to cardiogenic shock (CS).[4,15] CS is characterized by tissue hypoperfusion based on insufficient cardiac output due to primary cardiac dysfunction; typical signs are cold extremities, reduced urine output, impaired mental status, and (not mandatory) arterial hypotension.[15] Hyperlactataemia and decreased pH reflect the metabolic effects of the tissue hypoperfusion.[15] Despite extensive efforts in clinical commitment as well as research, in-hospital mortality remains as high as 33–65% in CS patients.[16,17]

Thus, the identification of AHF patients at risk for both WHF or CS is an unmet need; it would allow for a better patient surveillance and vigilance concerning these dangerous AHF trajectories. Previous studies have tried to identify stratify the risk of developing WHF: Renal function was found to be a potent predictor (especially blood urea nitrogen).[9,18] However, novel circulating biomarkers like pro-adrenomedullin need further exploration in this regard. On top, prediction of new-onset CS requires to be addressed. Therefore, this study aims to assess the frequency and prediction of both WHF and new-onset CS in this contemporary population of hospitalized AHF patients.

Methods

Study design

Observational, prospective, single centre study in unselected patients presenting with AHF. Systematic follow-up for WHF, CS, and death.

Definitions

1 Development of WHF was defined by the RELAX-AHF-2 trial criteria adjusted for this study's setting.[10] WHF was present if any of the following criteria was true:

a Initiation or increased dose of intravenous diuretics during hospitalization with the exception of initiation of intravenous diuretic treatment at enrolment.
b Initiation or increased dose of intravenous heart failure medication with the exception of initiation of intravenous heart failure medication treatment at enrolment.
c Implementation of any mechanical circulatory support.
d Invasive ventilation.
e Initiation of any renal replacement therapy.

2. New-onset CS was defined by SCAI (cardiogenic shock classification by the Society for Cardiovascular Angiography and Interventions) stage A at enrolment and progression to any higher SCAI stage during the hospital stay.

Since January 2022, SCAI staging is performed prospectively by clinicians. For patients enrolled before, staging was done in retrospect with consultation of clinical notes, registered vital signs, laboratory values, and therapeutic decisions.

Study population

Patients with AHF were enrolled in our on-going single tertiary care centre, prospective cohort study CYCLE (Characterisation of phenotYpes in aCute heart faiLure patiEnts), recruiting since 2019. To be eligible for inclusion, patients had to present with NT-proBNP (N-terminal prohormone of brain natriuretic peptide) $\geq$ 300 pg/mL and a new onset or severe worsening of heart failure symptoms within the last 7 days (at least 3 out of 6 symptoms of heart failure had to be present; e.g., orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, pulmonary rales, peripheral oedema, and gut congestion). Other medical conditions explaining the abovementioned symptoms, malignancies with a life expectancy $<$ 12 months, and age $<$18 years were exclusion criteria. All patients provided written informed consent. The study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee (study identifier PV5983).

Baseline characteristics

Continuous variables are shown as medians (1st quartile, 3rd quartile) and compared using the Mann–Whitney *U*-test. Binary variables are shown as counts (frequencies after exclusion of missing values) and compared using Fisher exact test. Missing values were excluded for both tests.

Predictors of worsening heart failure and cardiogenic shock

In order to identify potential predictors of WHF and new-onset CS, suitable baseline parameters were assessed by fitting logistic regression models adjusted for age and sex. Exceptions: age was adjusted for sex only and vice versa; the end-inspiratory diameter of the inferior vena cava was also adjusted for tricuspid valve regurgitation. Age is displayed as per 10 years, blood pressures as per 10 mmHg, and heart rate per 10 b.p.m. The following parameters were logarithmized because of skewed distribution for further

statistical analysis: serum creatinine, CRP (C-reactive protein), procalcitonin, NT-proBNP, bilirubin, and mid-regional pro-adrenomedullin. Firth Penalization was used in logistic regression to predict new onset CS with sex, acute myocardial infarction, LVEF (left ventricular ejection fraction) $\geq$ 40%, and the end-inspiratory diameter of the inferior vena cava.

In-hospital mortality regressions

WHF and new-onset CS were tested as predictors of in-hospital mortality by applying logistic regression models with Firth Penalization adjusted for age and sex.

Statistic software

All computations were performed using R version 4.1.2.

Results

Baseline characteristics

Overall, 223 patients were included (baseline characteristics shown in *Table 1*). Median age was 78 years (1st quartile 67, 3rd quartile 83), 80 were women (35.9%). The median body mass index was 27.5 kg/m^2 (24.0, 31.7). Frequent co-morbidities were: arterial hypertension (164, 73.5%), diabetes mellitus (78, 35.0%), prior myocardial infarction (76, 34.1%), atrial fibrillation (138, 62.2%), COPD (chronic obstructive pulmonary disease; 21, 9.8%), and pulmonary arterial hypertension (22, 10.0%). Chronic kidney disease was diagnosed in 89 patients (39.9%): 5 (2.2%) in stage, 6 (2.7%) in stage 2, 39 (17.5%) in stage 3, 11 (4.9%) in stage 4 and 2 (0.9%) in stage 5. Ischaemic cardiomyopathy was present in 82 patients (40.8%). In the past 2 years, 70 (33.0%) were hospitalized for AHF once or twice, 50 (23.6%) more than twice. Common triggers for the current AHF event were atrial fibrillation (67, 30.3%), rise in blood pressure (60, 27.6%), infections (50, 22.7%), and acute myocardial infarction (29,

Table 1 Patient characteristics of all included patients

	All (N = 223)		All (N = 223)
Baseline data		Laboratory	
Age (years)	78.0 (67.0, 83.0)	pH	7.4 (7.3, 7.4)
Sex (female) (%)	80 (35.9)	Lactate (mmol/L)	1.6 (1.2, 2.1)
Co-morbidities and medical history		Haemoglobin (g/dL)	12.5 (10.7, 13.8)
Arterial hypertension (%)	164 (73.5)	Bilirubin (mg/dL)	0.7 (0.4, 1.3)
Prior myocardial infarction (%)	76 (34.1)	ASAT (U/L)	30.0 (22.0, 42.8)
Atrial fibrillation (%)	138 (62.2)	ALAT (U/L)	26.5 (18.0, 38.1)
Diabetes mellitus (%)	78 (35.0)	Serum creatinine (mg/dL)	1.5 (1.1, 2.1)
Chronic kidney disease (%)	89 (39.9)	Cystatin c (mg/L)	1.9 (1.4, 2.4)
COPD (%)	21 (9.8)	CRP (mg/L)	12.0 (5.0, 35.0)
Pulmonary arterial hypertension (%)	22 (10.0)	Procalcitonin (μg/L)	0.1 (0.0, 0.1)
Heart failure history		NT-proBNP (ng/L)	7254.0 (3446.8, 14 720.2)
Ischaemic cardiomyopathy (%)	82 (40.8)	Pro-adrenomedullin (nmol/L)	2.0 (1.4, 2.9)
Heart failure hospitalizations (2 years): 1–2	70 (33.0)	INR	1.2 (1.1, 1.6)
Heart failure hospitalizations (2 years): > 2	50 (23.6)	SCAI at enrolment	
Trigger of acute heart failure		SCAI A (%)	186 (84.2)
Acute myocardial infarction (%)	29 (13.1)	SCAI B (%)	18 (8.1)
Tachyarrhythmia (%)	67 (30.3)	SCAI C (%)	17 (7.7)
Hypertensive crisis (%)	60 (27.6)	SCAI D (%)	0 (0.0)
Infection (%)	50 (22.7)	SCAI E (%)	0 (0.0)
Clinical presentation		Echocardiography	
Systolic blood pressure (mmHg)	140.0 (117.0, 159.0)	LVEF $\leq$ 40% (%)	109 (61.2)
Diastolic blood pressure (mmHg)	77.0 (67.0, 90.0)	TAPSE (mm)	16.5 (12.9, 20.9)
Heart rate (b.p.m.)	83.0 (71.0, 103.8)	No TR (%)	21 (11.3)
NYHA state: I or II (%)	8 (3.6)	Mild TR (%)	98 (52.7)
NYHA state: III (%)	91 (41.2)	Moderate TR (%)	34 (18.3)
NYHA state: IV (%)	122 (55.2)	Severe TR (%)	33 (17.7)
		End-inspiratory inferior vena cava diameter (mm)	16.0 (10.0, 22.0)

All: all patients considered in this analysis (N = 233). For binary variables absolute and relative frequencies are given. Relative frequencies calculated excluding missing values. For continuous variables median (1st quartile, 3rd quartile) is given.
ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; INR, international normalized ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association functional classification of heart failure; pro-adrenomedullin, mid-regional pro-adrenomedullin; SCAI, cardiogenic shock classification by the Society for Cardiovascular Angiography and Interventions, ranging from A (at risk) to E (in extremis); TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid valve regurgitation.

13.1%). Regarding left ventricular function, 109 patients (61.2%) presented with a LVEF ≤ 40%; 213 patients (96.4%) had dyspnoea according to NYHA (New York Heart Association functional classification of heart failure) III or IV. Median systolic blood pressure at presentation was 140 mmHg (117, 159), diastolic blood pressure 77 mmHg (67, 90), heart rate 83 b.p.m. (71, 104), pH 7.4 (7.3, 7.4), lactate 1.6 mmol/L (1.2, 2.1), creatinine 1.5 mg/dL (1.1, 2.1), NT-proBNP 7254 pg/mL (3446.8, 14 720.2), and mid-regional pro-adrenomedullin 2.0 nmol/L (1.4, 2.9). At enrolment, 186 (84.2%) patients presented with SCAI stage A, 18 (8.1%) with B and 17 (7.7%) with stage C; no SCAI D or E was registered at this time.

Baseline characteristics stratified by WHF and new-onset CS, respectively, are provided in *Table*s S1 and S2. Grading of tricuspid valve regurgitation at baseline and discharge including changes over the course of hospitalization are displayed in Table S3. The median duration of hospitalization was 9 days (6, 13).

Prevalence and prediction of worsening heart failure

Of all patients, 96 (44.2%) developed WHF. Chronic kidney disease [odds ratio, OR 2.20 (95% confidence interval: 1.25, 3.93), P = 0.007], logarithmized serum creatinine [OR 2.90 (1.51, 5.82), P = 0.002], cystatin c [OR 1.86 (1.27, 2.77), P = 0.002], moderate or severe tricuspid valve regurgitation [OR 2.08 (1.11, 3.94), P = 0.023], and logarithmized mid-regional pro-adrenomedullin [OR 3.01 (1.75, 5.38), $P < 0.001$] were significant predictors of WHF (*Figure 1*).

Not significantly associated with WHF proved to be (among others): age per 10 years [OR 0.87 (0.70, 1.06), P = 0.17], number of hospitalization for heart failure in the last 2 years [for > 2 events: OR 1.48 (0.73, 3.02), P = 0.28], systolic blood pressure per 10 mmHg [OR 0.91 (0.83, 1.00), P = 0.052], NYHA stage [for NYHA I/II combined with NYHA IV as reference level: OR 0.89 (0.21, 3.81), P = 0.87], triggers of the current AHF event [for acute myocardial infarction: OR 1.46 (0.66, 3.26), P = 0.35], creatinine in spot urine [OR 1.41 (0.94, 2.94), P = 0.33], albumin in spot urine [OR 1.00 (1.00, 1.00) P = 0.20], logarithmized high-sensitive troponins [T: OR 1.00 (1.00, 1.01), P = 0.28; I: OR 1.00 (1.00, 1.00), P = 0.50], logarithmized bilirubin [OR 1.28 (0.91, 1.81), P = 0.16], logarithmized CRP [OR 1.07 (0.85, 1.35), P = 0.59], logarithmized procalcitonin [OR 1.27 (1.00, 1.64), P = 0.054], logarithmized NT-proBNP [OR 1.06 (0.81, 1.40), P = 0.65], and LVEF ≤ 40% [OR 0.61 (0.31, 1.16), P = 0.13].

Prevalence and prediction of new-onset cardiogenic shock

Overall, 18 (9.7%) patients exhibited new-onset CS; the majority remains at SCAI stage A (*Figure 2*). Chronic kidney disease [OR 3.17 (1.16, 9.58), P = 0.03], diastolic blood pressure per 10 mmHg [OR 0.68 (0.48, 0.91), P = 0.016], haemoglobin [OR 0.57 (0.41, 0.77), $P < 0.001$], logarithmized CRP [OR 1.55 (1.04, 2.34), P = 0.032], cystatin c [OR 1.88 (1.00, 3.53) P = 0.045], logarithmized mid-regional pro-adrenomedullin [OR 2.90 (1.19, 7.19), P = 0.019], and moderate or severe tricuspid valve regurgitation [OR 10.44 (2.61, 70.00), P = 0.003] were significantly associated with new-onset CS.

Logarithmized serum creatinine, on the other hand as a predictor of WHF, missed significance in prognostication of new-onset CS [OR 1.81 (0.57, 5.36), P = 0.29]. Once again, logarithmized NT-proBNP was not a significant predictor [OR 1.34 (0.80, 2.27), P = 0.27].

In-hospital mortality

Of all patients, 8/223 (3.6%) died in hospital. In the subset of patients with WHF, in-hospital mortality was 7.3% (7/96 patients deceased) and in those with new-onset CS 27.8% (5/18 patients deceased).

The presence of WHF increased the probability of in-hospital death by 6.64 times [OR 6.64 (1.21, 36.55), P = 0.03]; new-onset CS by 38.27 times [OR 38.27 (6.32, 231.81), $P < 0.001$] (*Figure 3*). Only 1/97 patient (1.0%) of those without WHF and new-onset CS died.

Discussion

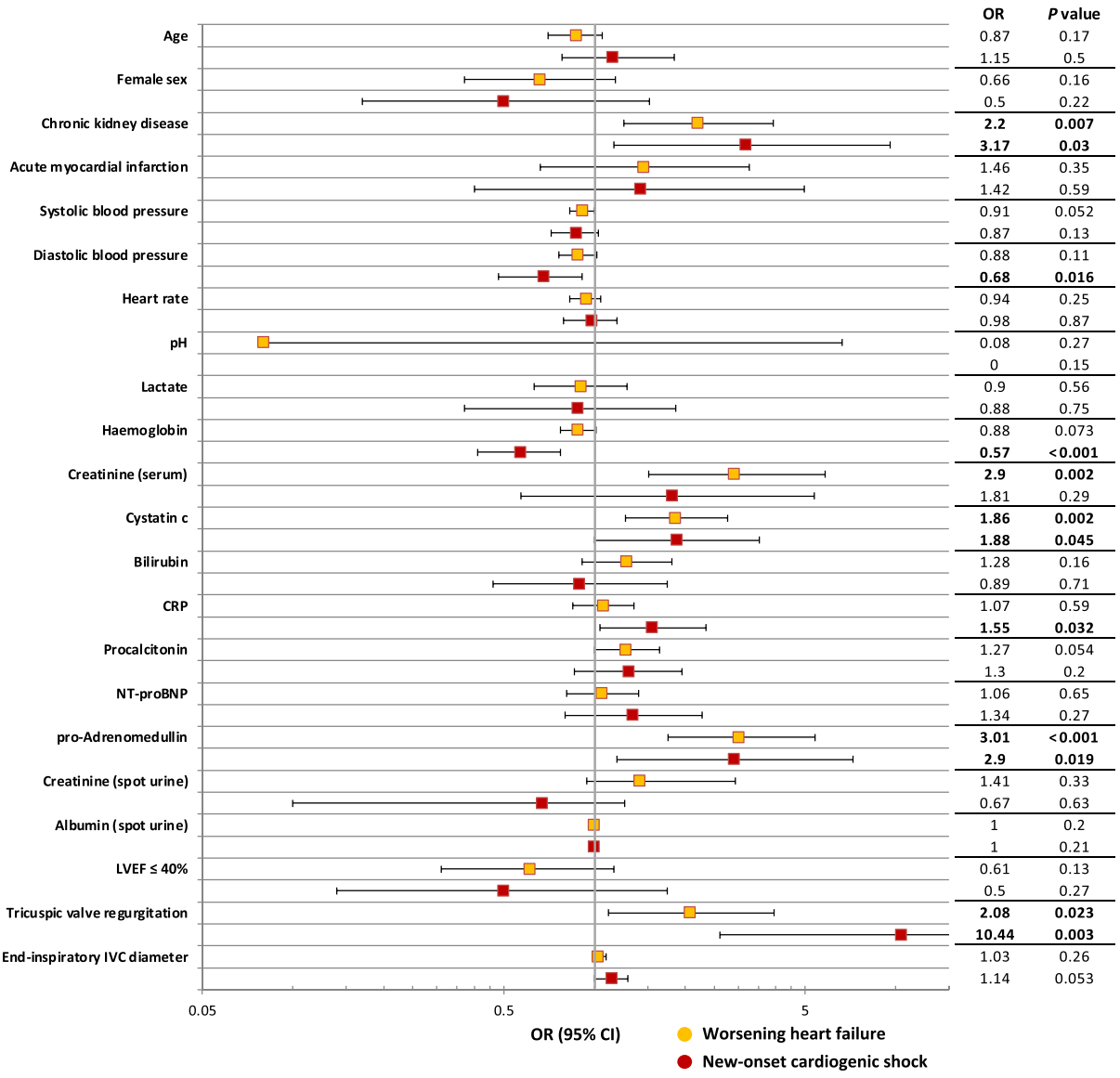
Worsening heart failure is common

In our population of unselected patients hospitalized for AHF at a German tertiary care centre, WHF (as defined by adjusted criteria of the RELAX-AHF-2 trial) was found to be highly frequent: 44% of patients fulfilled the criteria and presented with WHF.

It is noteworthy that this number exceeds by far the expected frequency based on the RELAX-AHF-2 trial. About 7–42% WHF in AHF patients was described in other populations.[8,11–14,18] In the RELAX-AHF-2 trial itself, WHF occurred in 7.3% of patients (of all patients, not stratified by intervention vs. placebo).[10]

This highlights that WHF in AHF patients is common but varies a lot depending on the exact definition.[7] Concerning the by far higher frequency of WHF events compared with

Figure 1 Predictors of worsening heart failure and cardiogenic shock. Acute myocardial infarction: as trigger of current AHF event. Serum creatinine, CRP, procalcitonin, NT-proBNP, bilirubin, and mid-regional pro-adrenomedullin were logarithmized. CRP, C-reactive protein; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OR (95% CI), odds ratio (95% confidence interval); pro-adrenomedullin, mid-regional pro-adrenomedullin; tricuspid valve regurgitation, moderate or severe.



the RELAX-AHF-2 trial, two reasons may be dominating: First, the initial dose finding of intravenous diuretics was left to the discretion of the treating physician, not all of them trained cardiologists (especially in the emergency department). Thus, too low doses at the beginning may have resulted in the commonly occurring need for dose escalation—herewith meeting the WHF criteria. Another reason may be the time of censoring: While RELAX-AHF-2 censored the registration of WHF events at day 5 (WHF rate: 7.3%), for example, Weatherley did so at day 7 (WHF rate: 29%) and Torre-Amione at day 30 (WHF rate: 42%).[8,10,11] This study, in contrast, censored at discharge from hospital and therefore covered the whole duration of the hospitalization.

Cardiogenic shock affects few, but with high impact

Overall, 9.7% of the hospitalized AHF patients in the present study developed a new-onset CS during their hospitalization. While this is still a minority, the impact on outcomes is strik-

Figure 2 SCAI trajectories during hospitalization. SCAI: cardiogenic shock classification by the Society for Cardiovascular Angiography and Interventions, ranging from A (at risk) to E (in extremis).

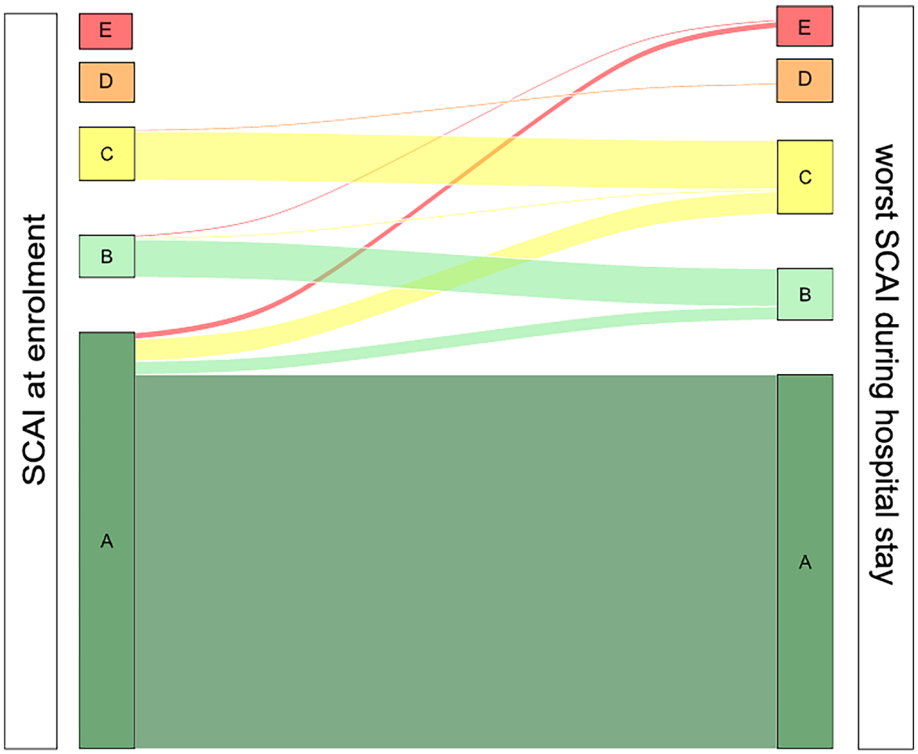
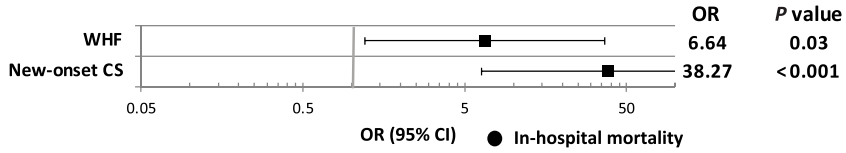


Figure 3 Association of WHF and new-onset CS with in-hospital mortality. Both end points correlate significantly with in-hospital mortality. OR (95% CI), odds ratio (95% confidence interval).



ing: The overall AHF in-hospital mortality amounts to 4–10%.[3,4] When only taking into account the subset of CS patients, in-hospital mortality rises to 33–65%.[16,17,19] These numbers emphasize the striking need for identification of AHF patients at risk for CS development. This would allow for more vigorous surveillance, treatment escalation when needed and vigilance regarding these dangerous disease trajectories in general.

Prediction of worsening heart failure and cardiogenic shock is challenging

In the assessment of potential baseline predictors of WHF and new-onset CS, chronic kidney failure (as well as elevated cystatin c and, at least regarding WHF, serum creatinine), moderate or severe tricuspid valve regurgitation and mid-regional pro-adrenomedullin proved to be significantly associated with both endpoints. In particular, kidney failure has been described before as a potent predictor of WHF.[18] Overall prediction remains challenging, though, with moderate C-indices for multivariable prediction models.[9]

Impaired renal function reduces the capacity to regulate volume overload. Furthermore, acute (on chronic) kidney failure is likely to be present early in the CS unfolding and may therefore be useful in its timely diagnosis or prediction, respectively. It is a strong predictor of mortality in CS.[20] On the downside, with a rather high chronic kidney disease frequency of 39.9% in the overall population of this study, this parameter alone may not be a suitable discriminator. Regression analyses stratified by chronic disease stages were not possible due to the limited dataset, though.

Albuminuria was shown to be associated with more congestion, higher 2-year mortality and more frequent rehospitalization and was strongly correlated to NT-proBNP.[21] In this study, though, albumin in spot urine was not able to predict WHF and new-onset CS during the current hospitalization. On top, the same is true for NT-proBNP as a well-established marker of congestion. Thus, albuminuria might be more valuable in long-term risk stratification as opposed to short-term outcomes. These findings could be hampered by the limited dataset, though.

Tricuspid valve regurgitation: Marker of valvular right heart failure

Interestingly, moderate or severe tricuspid valve regurgitation (TR) was strongly associated with both WHF and new-onset CS in accordance with our clinical experience. This finding highlights once again that heart failure comprises not only systolic left ventricular dysfunction but should be perceived and treated as a more comprehensive disease. Right heart failure is even described as a modifier of mortality risk in the overall AHF population.[4]

It is worth contemplating if the regurgitation itself or rather its underlying disease is the real problem: TR may be caused by structural abnormalities of the valve itself (primary regurgitation), by increased right ventricular afterload (in most cases due to left ventricular dysfunction and resulting pulmonary hypertension; secondary regurgitation) or may even occur independent from such pathologies (isolated regurgitation). The association of higher grades of TR with unfavourable clinical outcomes independent from other pathologies has been demonstrated before in several different settings.[22–24] Nevertheless, right ventricular dysfunction, characterized rather by reduced TAPSE (tricuspid annular plane systolic excursion) than right ventricular dilatation, remains a strong modifier of risk.[25] As a consequence, surgery is recommended in severe primary TR and in secondary TR when left-sided surgery is performed anyway.[26] The benefit of surgery compared with medical treatment in all other cases remains disputed.[26] On top, percutaneous interventional approaches are currently under intense investigation: An observational, comparative, propensity score matched study found a decreased risk of death and heart failure rehospitalization in those patients who underwent the intervention compared with those under medical treatment only.[27] This finding is challenged by the recently published TRILUMINATE trial, which showed a benefit in terms of quality of life, but not mortality or heart failure hospitalization at 1 year of follow-up—further follow-up to 5 years is planned, though, and the trial might have been underpowered.[28] More randomized controlled trials are already ongoing to improve the evidence base.

Mid-regional pro-adrenomedullin: a biomarker of interest?

Adrenomedullin is a circulating biomarker particularly known for its role in maintaining endothelial integrity and vasodilatation.[29] In the context of heart failure and the associated congestion, adrenomedullin levels are increased—probably as a response to prevent further tissue volume overload.[29–32] Elevated adrenomedullin levels are also known to correlate with 1-year mortality[33]; as well as with all-cause mortality during a median follow-up of 21 months and the combined endpoint with rehospitalization for heart failure in the BIOSTAT-CHF registry.[32]

In this study, the more stable mid-regional pro-adrenomedullin as the precursor of the biological active bio-adrenomedullin was assessed. It was found to be highly predictive of WHF and new-onset CS. This cannot be explained by only being a marker of congestion, as NT-proBNP showed no predictive value. It is likely that pro-adrenomedullin's role in sustaining vascular integrity is key to understand its worth in predicting WHF and CS development: Non-infectious inflammatory pathomechanisms and their impact on the endothelium are known both in CS as well as chronic heart failure, for example, heart failure with preserved ejection fraction (HFpEF).[34,35]

In summary, this is a strong call to further explore adrenomedullin as a circulating biomarker in heart failure patients.

Limitations

Attention should be paid to possible limitations of this study:

First, the follow-up was censored at discharge from hospital. It is known, though, that WHF and death frequently occurs in the early post-discharge period. This study design might therefore have led to underreporting of respective adverse events. A post-discharge follow-up is currently ongoing to address this issue in the future.

Second, the WHF definition was adapted from the RELAX-AHF-2 trial but without the strict treatment protocol of an interventional trial. Thus, for example, initial dose finding of intravenous diuretics was left to the discretion of the local physician (not all of them trained cardiologists or even heart failure specialists especially in the emergency department). This might possibly explain the unexpected high WHF frequency compared with RELAX-AHF-2 by insufficient initial doses followed by up-titration (and herewith meeting the WHF endpoint).

Third, assessing potential predictors of CS development was possibly hampered by the low absolute prevalence in this cohort. While its relative frequency was found to be as expected, the overall study cohort size is still rather small. For the same reason, regression analyses could be adjusted

for age and sex only. Thus, the present study may be underpowered for some analyses which constitutes a rather explorative character. On top, the predictive ability of circulating biomarkers like pro-adrenomedullin could be overestimated due to worse renal function in WHF and new-onset CS patients. This is just another call for expanding the database by the ongoing enrolment.

Conclusions

Roughly 44% of AHF patients experience WHF during hospitalization, and 10% even develop CS with its dismal prognosis. AHF patients with these events are at excess mortality risk. Kidney failure, tricuspid valve regurgitation and pro-adrenomedullin are predictors of both WHF and new-onset CS (*Central Illustration*) and could potentially serve as early warning signs of WHF and new-onset CS. In particular, pro-adrenomedullin and tricuspid valve regurgitation are of high interest, as further investigation of their interplay with WHF/new-onset CS might not only contribute to our understanding of the underlying pathomechanisms, but could even identify patients suitable for interventional treatment.

Clinical perspectives

Clinical competencies

- Worsening heart failure in patients hospitalized for acute heart failure is frequent and associated with excess mortality. Thus, caregivers should be vigilant to these patients at risk as early as possible.
- In particular, those patients with chronic kidney disease or moderate or severe tricuspid valve regurgitation are likely to experience worsening heart failure. They should be given special attention.
- Acute heart failure events are markers of a dangerous heart failure disease trajectory. Thus, medical therapy should be re-evaluated after decongestion and stabilization concerning optimizing heart failure drug administration, device evaluation as well as advanced (and palliative) care planning.

Translational outlook

- Pro-adrenomedullin is not yet established as a circulating biomarker in routine clinical care. It strongly correlated to worsening heart failure events, though, and should thus be further evaluated for its usefulness in terms of diagnostics as well as therapy surveillance in the heart failure context.
- Tricuspid valve regurgitation is a relevant risk factor of worsening heart failure events. It remains unknown, though, if its reduction by interventional therapy might reduce such events.

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Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1: Baseline characteristics stratified by development of WHF. All: all patients with information on WHF (N = 217). WHF: patients exhibiting worsening heart failure during hospitalisation according to modified RELAX-AHF-2 criteria (N = 96). No WHF: patients not exhibiting worsening heart failure during hospitalisation according to modified RELAX-AHF-2 criteria (N = 121). COPD: chronic obstructive pulmonary disease. LVEF: left ventricular ejection fraction. NYHA: New York Heart Association functional classification of heart failure. ASAT: aspartate aminotransferase. ALAT: alanine aminotransferase. CRP: C-reactive protein. NT-proBNP: N-terminal prohormone of brain natriuretic peptide. Pro-Adrenomedullin: mid-regional pro-adrenomedullin. INR: international normalised ratio. SCAI: cardiogenic shock classification by the Society for Cardiovascular Angiography and Interventions, ranging from A (at risk) to E (in extremis). For continuous variables median (1st quartile, 3rd quartile) is given. For binary variables absolute and relative frequencies are given. *P* values given for WHF vs. no WHF. Relative frequencies calculated excluding missing values.

Table S2: Baseline characteristics stratified by development of CS. All: all patients with information on CS development (N = 185) and exclusion of all patients with SCAI stage > A at enrolment. CS: patients developing cardiogenic shock during hospitalisation according to the SCAI classification (N = 18). No CS: patients not developing cardiogenic shock during hospitalisation according to the SCAI classification (N = 167). COPD: chronic obstructive pulmonary disease. LVEF: left ventricular ejection fraction. NYHA: New York Heart Association functional classification of heart failure. ASAT: aspartate aminotransferase. ALAT: alanine aminotransferase. CRP: C-reactive protein. NT-proBNP: N-terminal prohormone of brain natriuretic peptide. Pro-Adrenomedullin: mid-regional pro-adrenomedullin. INR: international normalised ratio. SCAI: cardiogenic shock classification by the Society for Cardiovascular Angiography and Interventions, ranging from A (at risk) to E (in extremis). For continuous variables median (1st quartile, 3rd quartile) is given. For binary variables absolute and relative frequencies are given. *P* values given for CS vs. no CS. Relative frequencies calculated excluding missing values.

Table S3: Course of tricuspid valve regurgitation.

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