IJC Heart & Vasculature 52 (2024) 101424

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Biomarker patterns in patients with cardiogenic shock versus septic shock

Elma J. Peters [a,1], Martin S. Frydland [b,1], Christian Hassager [b], Lieuwe D.J. Bos [c], Lonneke A. van Vught [d], Olaf L. Cremer [e], Jacob E. Møller [b,f], Bert-Jan H. van den Born [g], Alexander P.J. Vlaar [d], Jose P.S. Henriques [a,*], on behalf of the MARS consortium

[a] Department of Cardiology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands
[b] Department of Cardiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[c] Intensive Care, Department of Respiratory Medicine, Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands
[d] Department of Intensive Care Medicine & Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands
[e] Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, the Netherlands
[f] Department of Cardiology, Odense University Hospital, Odense, Denmark
[g] Department of Internal/vascular Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Cardiogenic shock
Septic shock
Biomarkers
Mortality

ABSTRACT

Background: In cardiogenic shock (CS), contractile failure is often accompanied by a systemic inflammatory response syndrome. In contrast, many patients with septic shock (SS) develop cardiac dysfunction. A similar hemodynamic support strategy is often deployed in both syndromes but it is unclear whether this is justified based on profiles of biomarkers expressing neurohormonal activation and cardiovascular stress.
Methods: In this prospective, multicenter cohort, 111 patients with acute myocardial infarction related CS were identified, and matched to patients with SS. Clinical parameters were collected and blood samples were obtained on day 1–3 of Intensive Care admission.
Results: In this shock cohort comprising 222 patients, with a mean age of 61 (±13.5) years and of whom 161 (37 %) were male, we found that despite obvious clinical disparities on admission, mortality at 30-days did not differ (CS: 40.5 % vs. SS 43.1 %, p = 0.56). Overall, plasma concentrations of all biomarkers were higher in SS patients, with the largest difference on the first day. However, only in CS patients the biomarker concentrations were associated with mortality.
Conclusion: In this prospective, multicenter cohort SS and CS patients showed similarities in baseline conditions and had similar mortality. However, several biomarkers only showed prognostic value in CS.

1. Introduction

Cardiogenic shock (CS) is a devastating clinical condition with a high mortality up to 50 %. [1] Apart from early revascularization very little has been shown to improve clinical outcome in these patients. [2] It is therefore important to find clinical markers that may help to understand the CS syndrome. Although CS is primarily characterized by loss of myocardial contractility leading to hypoperfusion, it is often complicated with a systemic inflammatory response syndrome (SIRS-) like response, caused by activation of the neurohormonal cascade secondary to hypoperfusion of organs. [3] Several studies have shown that CS patients with SIRS or sepsis have a higher risk of death than CS patients in whom this cascade has not been activated. [4–7] Additionally, in septic shock (SS), up to half of the patients show potential reversible systolic or diastolic cardiac dysfunction, which is associated with poor outcome in SS patients. [8,9]

Despite being admitted with different shock etiologies, both CS and SS patients are critically ill from a clinical, biochemical and hemodynamical perspective and the phenotype of shock may be more mixed within days after hospitalization. Furthermore, patients are often supported in an identical manner in terms of pharmacologic hemodynamic support. It has already been demonstrated that biomarkers that are

* Corresponding author at: Amsterdam University Medical Center, Department of Cardiology, Meibergdreef 9 1105 AZ, Amsterdam, the Netherlands.
E-mail address: j.p.henriques@amsterdamumc.nl (J.P.S. Henriques).
[1] These two authors contributed equally.

https://doi.org/10.1016/j.ijcha.2024.101424
Received 2 February 2024; Received in revised form 11 April 2024; Accepted 7 May 2024
Available online 14 May 2024

known to be elevated in sepsis, also may be increased in CS patients. [10–14] However, it is unclear whether the level of activation and the increase in biomarkers are comparable between CS and SS patients and whether they have the same association with outcome. This could be of interest as is it not yet established whether these biomarkers should be used for clinical guidance. Therefore, the primary goal for this study was to compare consecutive CS patients and matched SS patients on levels and course of different biomarkers and their association with clinical outcome.

2. Materials and methods

2.1. Design and populations

The study was part of the *Molecular Diagnosis and Risk Stratification of Sepsis* (MARS) project, a prospective observational cohort study in the mixed ICUs of two tertiary teaching hospitals (NCT01905033). [15] All patients older than 18 years admitted to the two ICUs between January 2011 and January 2014 were included, with the exemption of elective cardiac surgery patients. For the current study, all patients admitted with cardiogenic shock due to ST-elevation myocardial infarction (STEMI) between January 2011 and September 2013 were screened, and included if they were revascularized by means of percutaneous coronary intervention (PCI). Subsequently, these patients were matched with SS patients from the MARS cohort by age and sex in a 1:1 ratio.

Cardiogenic shock was defined as: sustained hypotension (systolic blood pressure < 90 mmHg) and/or usage of inotropes / vasopressors and/or mechanical circulatory support for hypotension for more than 30 min on admission to the ICU. Septic shock was defined as: the presence of an infection diagnosed within 24 h after ICU admission in combination with the use of noradrenaline in a dose of more than 0.1 μg/kg/min and/or mechanical circulatory support for hypotension during at least 50 % of the ICU day.

2.2. Sample size and matching

As a comparison on biomarkers between the two etiologies of shock was not investigated priorly, the current study was exploratory in nature. To have the best available statistical power, all CS patients with blood samples available were included and compared to matched SS patients in a 1:1 ratio. Matching was done on age (range: ± 3 years) and sex.

2.3. Study parameters

Clinical parameters included hemodynamic parameters (e.g. mean arterial pressure [MAP], heart rate [HR], central venous pressure [CVP]), the extent of organ failure (measured with the Sequential Organ Failure Assessment [SOFA] score) and were retrieved from the electronic patient file.

A selection for various biomarkers was made based on contemporary literature. We focused on different systems to investigate their prognostic value for clinical outcome. Blood samples for biomarker analyses were obtained every morning on day 1, 2, and 3 after ICU admission. (Surrogates for) the following biomarkers were chosen, reflecting:

I. **Cardiovascular stress:** Atrial natriuretic peptide (ANP)
II. **Neurohormonal status:** Copeptin, adrenomedullin (ADM), endothelin-1 (ET-1)
III. **Inflammation:** C-reactive protein (CRP)
IV. **Tissue hypoperfusion:** Lactate
V. **Renal function:** Creatinine

For reliable results, stable surrogates were measured with assays from Thermo Fischer Scientific for ADM, ANP and ET-1; mid-regional pro-adrenomedullin (MRproADM), mid-regional pro-atrial natriuretic peptide (MRproANP) and C-terminal proendothelin-1 (CTproET1) respectively. [16–19]

2.4. Statistical analysis

Baseline characteristics of CS and SS patients were compared using the Chi-squared test (categorical data), Student's *t*-test (continuous normally distributed data) or Mann-Whitney *U* test (continuous not normally distributed data). Data were presented as mean (SD), median (IQR), and proportions (n [%]).

30-day all-cause mortality was presented with Kaplan–Meier curves and compared with the log-rank test. Days alive and out of ICU at 30 was calculated as 30, minus the total amount of days spent in the ICU within these 30 days for patients who survived until 30 days. People who deceased in the ICU automatically had zero days alive and out of ICU. This was also calculated on 60 days.

For comparing survival distributions between high versus low biomarker levels, a median-split was performed for each individual biomarker, measured on the first day of admission, in each shock group. This was done for SOFA-scores on admission in a similar fashion.

Sequential analyses of biomarkers and clinical parameters were conducted using repeated-measures mixed models with an unstructured covariance structure. The models included the shock group (CS or SS), time, and the interaction term between shock groups and time. The fixed type-3 effect of the interaction between shock group and time are reported. Non-gaussian distributed data were log-transformed for normalisation before insertion in the model. A p-value < 0.05 was considered statistically significant. Missing data were not imputed. Statistical analyses were performed using SAS Enterprise software version 7.4 (SAS Institute, Cary, NC, USA). A two-sided p-value < 0.05 was considered significant throughout.

2.5. Ethical approval

Patients were included via an opt-out consent method approved by the institutional review boards of both hospitals (IRB No. 10-056C). Participants were informed about the study by a brochure provided at ICU admission with an opt-out card that could be completed by the patient or legal representative in case of unwillingness to participate.

3. Results

3.1. Patients

From all patients in the MARS cohort, 111 were identified with

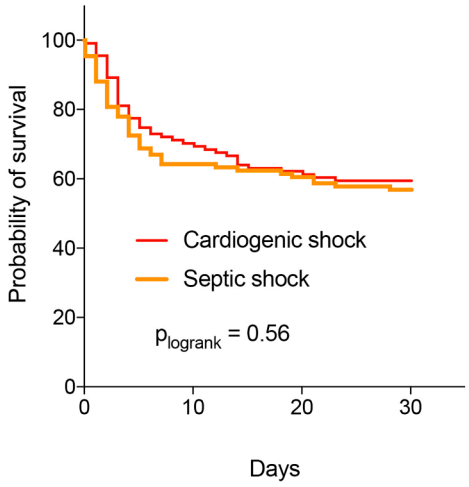

Fig. 1. 30-Day survival for cardiogenic shock and septic shock.

STEMI and CS treated by PCI. They were matched to 111 SS patients. (See Fig. 1 in suppl. for flow-chart).

Baseline characteristics were quite similar in both groups, but patients with CS had a higher BMI (27 [±4.6] vs 25 [±4.6] kg/m^2, p = 0.01), more often were smokers (16 % vs. 5 %, p = 0.01) and suffered from prior myocardial infarction more often (17 % vs. 8 %, p = 0.04) whereas SS patients more frequently had COPD (17 % vs. 3 %, p < 0.001) and chronic renal insufficiency (11 % vs. 4 %, p = 0.04) (Table 1). Of all CS patients, 61 % (n = 68) presented with an out-of-hospital cardiac arrest. SS patients were diagnosed with septic shock with different sources of infection, the main being pulmonary (31 %) and gastro-intestinal (31 %).

3.2. Clinical course

Hemodynamic parameters and SOFA scores are shown in Table 2 **and suppl.** Fig. 2. All SS patients were mechanically ventilated at ICU admission (vs. 95 % in CS) and the PaO_2/FiO_2 ratio was significantly higher in SS patients (152 vs. 110, p = 0.008). Absolute values for MAP were slightly higher in CS patients for all three days whereas the median heart rate was lower throughout this entire period. SOFA subscore for circulation, however, was 4 for the majority of CS patients, indicating that they received high dose catecholamines whereas SS patients scored lower for circulation. [20]. The CVP was similar for both shock groups. The SOFA score was higher for SS patients throughout the three days and they had a longer median length of stay in the ICU compared to CS patients [5 vs. 4 days, p = 0.002).

3.3. Mortality

Similar 30-day all-cause mortality was seen in SS and CS (43.1 % and 40.5 % respectively, p = 0.56) (Fig. 1). Of patients who died within 30 days, the vast majority died in the ICU (CS: 82.2 % vs SS: 89.4 %, p = 0.33). The median time to death for patients who died within 30 days was similar for both groups (CS: 3.0 days vs SS: 2.5 days, p = 0.21). Days alive and out of ICU at 30 days was 0 (0–21) for SS patients and 24 (0–27) for CS patients. At 60 day this was 28 (0–51) and 54 (0–57) days respectively, thereby showing a significant difference at both time points to the disadvantage of septic shock. Survival to hospital discharge differed significantly (47 % in SS, 61 % in CS, p = 0.03).

Table 1
Baseline characteristics.

	Septic shock (n = 111)	**Cardiogenic shock** (n = 111)	**p-value**
Age, mean (SD)	61 (14)	62 (13)	0.33
Male sex, n(%)	72 (65)	89 (80)	0.01
BMI, mean (SD)	25 (4.6)	27 (4.6)	0.01
Chronic cardiovascular insufficiency, n (%)	6 (5.4)	1 (0.9)	0.05
Chronic renal insufficiency, n (%)	12 (11)	4 (3.6)	0.04
COPD, n (%)	19 (17)	3 (2.7)	< 0.001
Diabetes, n (%)	25 (23)	14 (13)	0.05
Hypertension, n (%)	32 (29)	25 (23)	0.28
Previous myocardial infarction, n (%)	9 (8.1)	19 (17)	0.04
Congestive heart failure, n (%)	6 (5.4)	5 (4.5)	0.76
Current smoking status (yes), n (%)	6 (5.4)	18 (16)	0.01
Immune deficiency, n (%)	20 (18)	3 (2.7)	< 0.001
Malignancy, n (%)	21 (19)	3 (2.7)	< 0.001
Laboratory values on admission, median (IQR)			
Creatinine	141 (82 – 212)	112 (83 – 164)	0.01
CRP	170 (85 – 306)	27 (9 – 84)	< 0.001
Lactate	3.7 (2.0 – 9.5)	3.9 (2.6 – 7.2)	0.85
WBC	15.9 (9.2–21.5)	14.9 (12.1–18.7)	0.31
APACHE IV on admission	78 (62–116)	93 (77–116)	0.01

BMI = body mass index, kg/m^2; **COPD** = chronic obstructive pulmonary disease; **STEMI** = ST-segment elevated myocardial infarction; **Creatinin** in μmol/L; **CRP** = C-reactive protein, mg/L; **Lactate** in mmol/L; **WBC** = white blood cell count, x 10^9/L.

Table 2
Hemodynamic parameters and SOFA score, highest values on day 1–3 of ICU admission.

		Septic Shock Median (IQR)		**Cardiogenic Shock** Median (IQR)		**p-value**
Day 1	MAP	69	(62 – 77)	71	(67 – 81)	0.05
	HR	97	(83 – 116)	73	(59 – 85)	< 0.0001
	CVP	11	(7–17)	14	(9 – 17)	0.06
	SOFA	10	(8–14)	8	(6 – 9)	< 0.0001
Day 2	MAP	71	(65 – 79)	75	(69 – 85)	0.01
	HR	102	(86 – 114)	87	(77 – 105)	0.0003
	CVP	12	(8 – 16)	14	(10 – 18)	0.14
	SOFA	10	(8 – 15)	9	(7 – 11)	< 0.0001
Day 3	MAP	73	(70 – 81)	81	(73 – 91)	0.02
	HR	96	(83 – 111)	90	(75 – 104)	0.12
	CVP	12	(9 – 17)	12	(10 – 15)	0.41
	SOFA	11	(8 – 14)	8	(6 – 11)	0.0003

CVP = central venous pressure, mmHg; **SOFA** = sequential organ failure assessment; **MAP** = mean arterial pressure, mmHg; **Lactate** in mmol/L; **CRP** = c-reactive protein, mg/L; **Creatinine** in μmol/L.

3.4. Biomarker levels

Biomarker measurements were available in 178, 165 and 105 patients on day 1, 2 and 3 of ICU admission, respectively. Compared to SS, the plasma concentrations of ADM, copeptin, ANP and ET-1 were lower in patients with CS on day 1–3 of ICU admission. Further, the temporal changes differed from those in SS patients (Fig. 2**).** The largest difference between the two groups was seen on day one and these differences gradually decreased during admission. The biomarker reflecting the largest difference was copeptin (64 % difference in medians on day 1) whereas there was more resemblance between SS and CS patients with regards to the serum levels for ANP (35 % difference on day 1).

Additionally, we found that in CS patients a trend towards a better survival rate was seen for values below the median concentration for every biomarker, though only statistically significant for ADM, lactate, CRP and creatinine **(**Fig. 3 **and suppl.** Fig. 3**).** This trend persisted when conducting a sensitivity analysis which excluded CS patients with lactate levels below 2.0 mmol/L (suppl. Fig. 4). In patients with septic shock a difference in survival distribution between biomarker quantiles was only seen in lactate but absent in all others **(**Fig. 4 **and suppl. figure 5).**

Lactate levels showed a declining course in both shock syndromes during the first three days. In CS however, an evident rise in CRP was seen, from 27 (9–84) mg/L on admission to 175 (111–246) mg/L on the third day (suppl. table 1). On all three days, creatinine levels were higher in patients with SS compared to CS, though only statistically significant on the first day.

4. Discussion

4.1. Main results

Our study reveals that patients with CS and SS show many similarities in terms of patient characteristics, 30-day mortality and hemodynamic parameters but distinct differences in the degree of neurohumoral and inflammatory activation.

Regarding the baseline characteristics, CS patients more frequently had a history of cardiovascular disease and a higher cardiovascular risk. [21,22] Patients with SS however were more frequently immunocompromised and more often had COPD, making them more vulnerable to fulminant infections.[23] 30-Day mortality did not differ between groups and was around 40 %, which is in line with reports from other

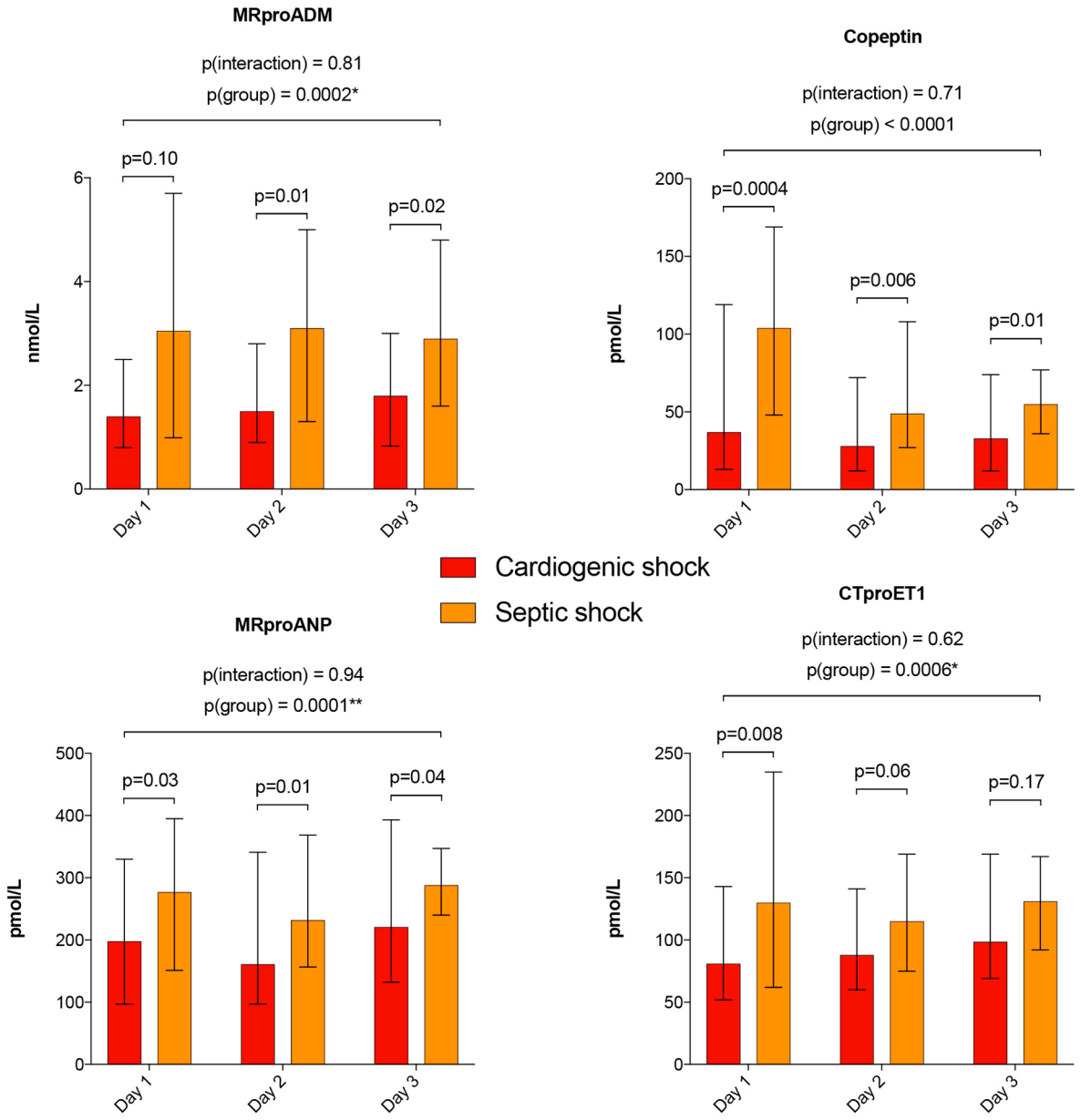

Fig. 2. Biomarker levels on the first 3 days of ICU admission, median + quartiles.

cohorts of patient with shock. [1,24,25].

During the first days of ICU admission, a significantly higher MAP was seen in the CS group. This is possibly pharmacologically induced since CS patients had higher SOFA circulation subscores, indicating that they received high dose catecholamines more often than SS patients. Median length of stay in the ICU was shorter for CS patients, also when corrected for mortality by means of calculating days alive and out of ICU. This indicates that when CS patients live through the first couple of days of admission, their time spent on the ICU is relatively short whereas patients with SS tend to stay in the ICU considerably longer.

4.2. Biomarkers investigated

Lactate is an intermediate product in the metabolism of carbohydrates and serves as a marker for tissue hypoperfusion. Creatinine serves as a marker of renal function and it has been demonstrated that creatinine clearance is independently associated with mortality in STEMI patients. [26] CRP is an acute phase reactant and the most commonly used biomarker for systemic inflammation.

Both ADM and ET-1 are produced by endothelial cells and play a major role in vasotonus. [27] Whereas ADM is an important vasodilator, ET-1 functions as a strong vasoconstrictor. ADM is released by various tissues in response to different hormonal and cytokine stimuli and can thus be considered as a marker for generalized cardiovascular stress, neurohormonal activation and inflammatory response. [28] Atrial natriuretic peptide, just like ADM, is a diuretic and natriuretic peptide. It is secreted by both atrial and ventricular cardiomyocytes in reaction to volume expansion and end-diastolic wall stress and has therefore widely been used as a marker for heart failure just like the generally used brain natriuretic peptide (BNP). [29] The choice to measure ANP was made because data suggest that it is released faster in response to cardiac ischemia whilst having a similar predictive value. [30] The neurohormone copeptin is a stable and sensitive surrogate marker for arginine vasopressine; a strong vasoconstrictor released in reaction to changes in plasma osmolality and hypovolemia.[31]

With endothelial activation being a hallmark of sepsis, both ADM and ET-1 have extensively been investigated in this context. [10] Both have shown markedly elevated levels in septic patients and correlate

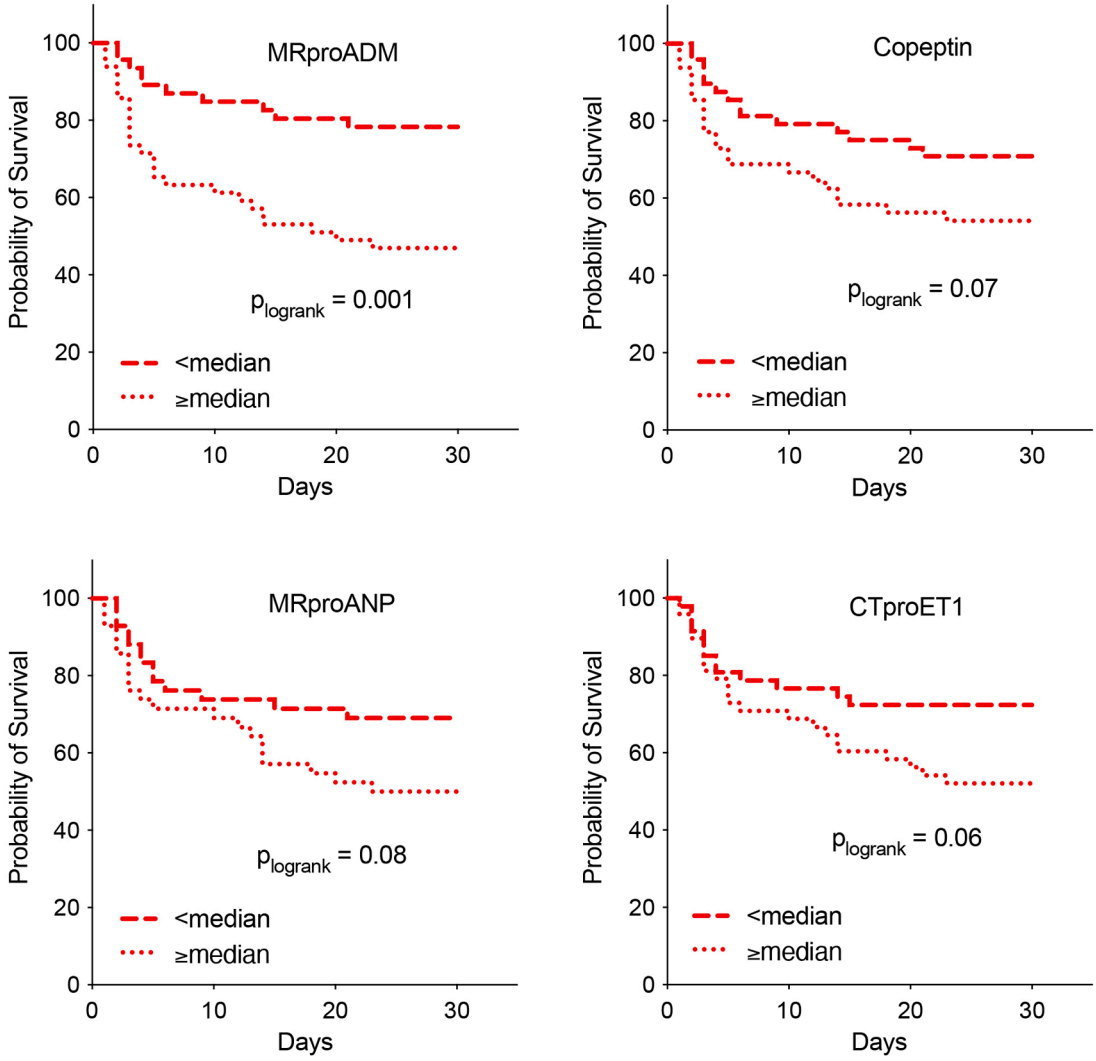

Fig. 3. 30-Day survival in cardiogenic shock for initial biomarker level on admission.

significantly with mortality, thereby functioning as a good biomarker for diagnosis and prognosis. [32–35] Both have also been found to be elevated in CS patients, results that even lead to the conduction of a randomized trial investigating adrenomedullin as a potential treatment target. [11,12,36,37] That same elevation is seen in our cohort and the association with mortality was found for both biomarkers in CS patients. The rise in ET-1 in CS patients from day one to three, suggests a loss of endothelial barrier function that increases over time and supports the hypothesis that disruption of the vascular integrity plays an important role in the pathophysiology of cardiogenic shock. The subgroup with higher ADM values corresponds to that with higher SOFA scores which could be expected from a generalized cardiovascular stress marker. Besides being a marker of heart failure, ANP has been demonstrated to correlate with organ dysfunction, sepsis, disease severity and mortality risk in critically ill patients admitted to the ICU. [38] Raised values were also demonstrated by both CS and SS patients in our cohort but the clear correlation with mortality was restricted to CS patients. Also for vasoconstrictor AVP, a strong correlation with mortality was found in patients with CS. This is in line with literature showing a correlation with poor outcomes in post-cardiac arrest patients. [39,40] Besides that, AVP is known to show a tremendous increase in both septic and hemorrhagic shock. [41] This increase is also seen in our SS patients.

Based on available literature we did expect to find a relationship between admission biomarker levels and mortality. However, this relation was only found in CS patients. A potential explanation for this could be that the day 1 measurements in SS patients are too late in the course of disease already, resulting in high measures in all patients, whereas the first measurement in cardiogenic shock might be able to distinguish for it's still early enough in the course of disease.

In our cohort, ADM was the biomarker with the strongest association with mortality in CS whilst in SS this biomarker had the weakest association. Potentially, the weak association of baseline ADM levels with mortality in SS is because vasodilatation is already present in sepsis. In CS however, the strong association of admission ADM level could identify patients with an inappropriate vasodilatation or patients in a different phase of the shock condition.

The results suggest that elevated biomarkers in CS patients indicate an increased systemic inflammatory response and correlate to worse outcomes whereas in SS they seem to be part of the natural course without the ability to differentiate between different outcomes, thus showing a prognostic "ceiling effect". It is remarkable that other studies did identify a correlation between mortality and levels of both ET-1 and ADM in septic patients. We hypothesize that this can partially be explained by differences in the population. The critically ill patients as described by Buendgens et al., have lower median SOFA scores and a lower mortality rate than the SS patients in our cohort. [32]

CRP in SS patients was considerably raised from the first day of ICU admission and reached its peak value on day 2 whereas CRP in values in CS patients increased gradually during ICU admission and a peak was not detected within 3 days. The most plausible explanation for this,

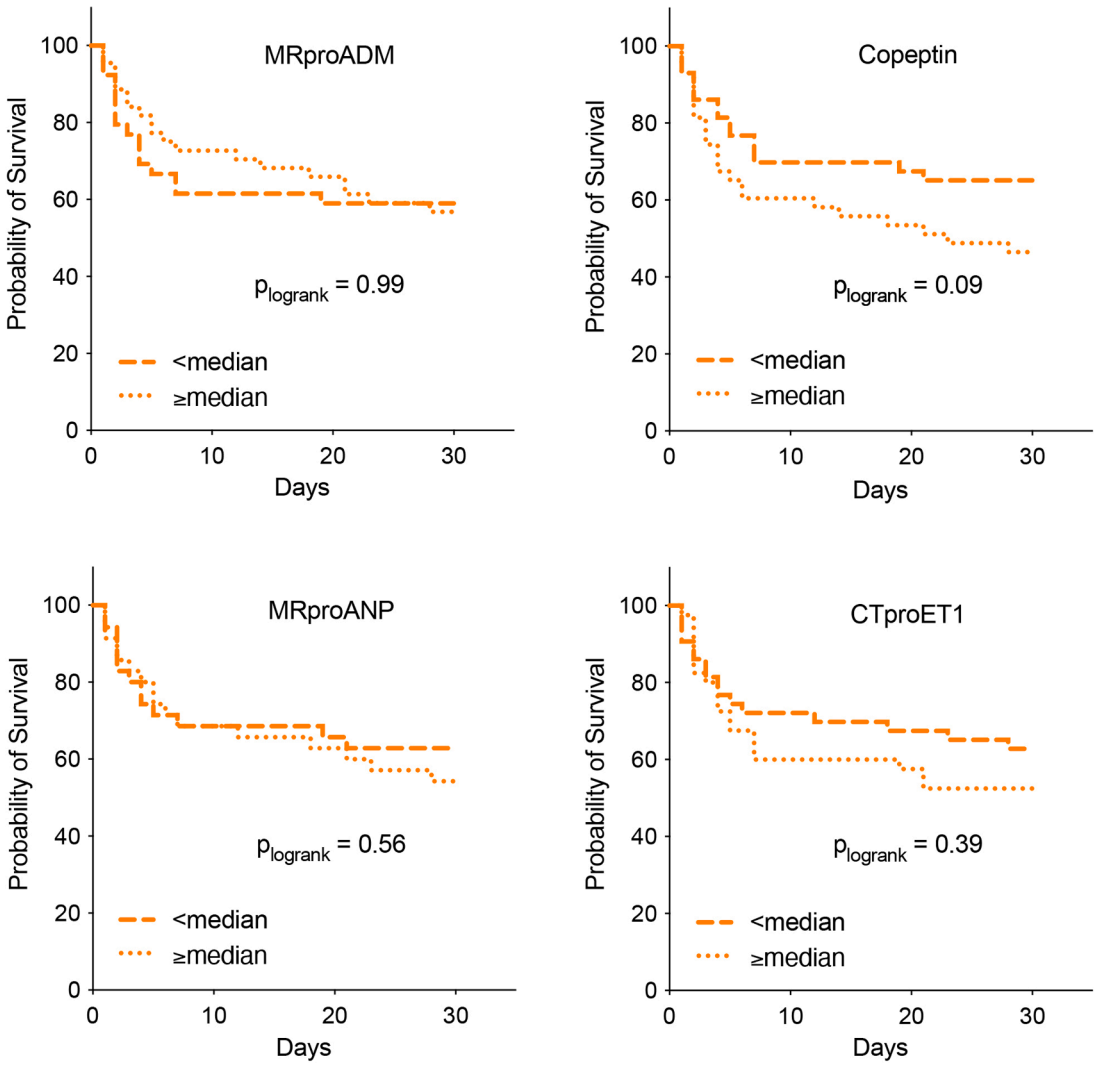

Fig. 4. 30-Day survival in septic shock for initial biomarker level on admission.

seems that SS develops in patients with longer standing infection. Their admittance to the ICU does not mark the first day of illness but the start of vital functions being at risk. Cardiogenic shock, especially when related to myocardial infarction and OHCA, leads to immediate ICU admission in most cases. In this group, the first day admission corresponds with the first day of illness. This could also explain the higher creatinine levels for SS patients on the first 3 days as their kidneys may have been exposed to a hypovolemic circulation for a longer period of time.

Despite the cohort and its samples being recruited approximately 10 years ago, we believe that the association between biomarkers and mortality remains applicable to the current era, as little has changed in clinical management practices. All cardiogenic shock patients were treated with primary PCI which is still the cornerstone treatment. [2] At most, a trend towards more culprit lesion-only PCI might be present but little changes in other medical treatment strategies have occurred. [42] With respect to the sepsis patients, more early awareness programs have been installed over time. Increased awareness and early intervention initiatives, such as the Surviving Sepsis Campaign may have influenced patient management slightly. [43,44] However, both patient groups were recruited in a tertiary center and we believe that the results may only remotely be influenced by the fact that the cohort has been collected 10 years ago.

4.3. Limitations

One of the limitations of our study concerns the definitions that were used to define both syndromes. As data from a larger study were used in a retrospective manner, no adaptions could be made in the definitions used. It would have been of interest to define SS according to a more contemporary definition and a SCAI stage of cardiogenic shock would facilitate comparison with other CS cohorts. [45]

As a results of performing a matching procedure, the cohorts automatically show more resemblance. Additionally, more homogeneity was created by including post cardiac arrest patients while post-cardiac arrest syndrome is characterized by inflammation. [46]

Data were collected as part of routine care which could have resulted in an increase in missing data and the lacking of some relevant information.

Furthermore, matching of the 111 CS patients to septic shock patients was performed by sex and age but unfortunately matching on sex failed in 17 cases. As the samples had been defrosted and analyzed this could not be resolved. We do however believe that this is of negligible influence of our findings.

Finally, in both hemodynamic parameters and biochemical measurements immortal time bias might have occurred. This implies that patients who deceased before days 3 (i.e. the worst patients), did not contribute to study outcomes anymore, potentially leading to a distorted image of the results on day 2 and 3. Nevertheless, this does not change

the main message as the associations with mortality were performed with biomarker levels on admission.

5. Conclusion

In this prospective, multi-center cohort we found that SS and CS patients were comparable on baseline, hemodynamic parameters and mortality. Even though admission levels of measured biomarkers were higher in patients with SS, they only showed a significant association with mortality in CS. The selected biomarkers in our study therefore seem appropriate for guiding clinical practice in CS patients, but may offer less added value for patients with SS.

CRediT authorship contribution statement

Elma J. Peters: Writing – original draft, Methodology, Formal analysis. **Martin S. Frydland:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Christian Hassager:** Writing – review & editing, Conceptualization. **Lieuwe D.J. Bos:** Writing – review & editing, Project administration, Conceptualization. **Lonneke A. van Vught:** Writing – review & editing, Project administration, Conceptualization. **Olaf L. Cremer:** Writing – review & editing, Conceptualization. **Jacob. E. Møller:** Writing – review & editing, Conceptualization. **Bert-Jan H. van den Born:** Writing – review & editing, Conceptualization. **Alexander P.J. Vlaar:** Writing – review & editing, Supervision, Conceptualization. **Jose P.S. Henriques:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was performed within the framework of the Center for Translational Molecular Medicine (CTMM) (www.ctmm.nl), project Molecular Diagnosis and Risk Stratification of Sepsis (Grant 04I-201). Members of MARS consortium are:

Departments of Intensive Care Medicine, Amsterdam University Medical Centers, location Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands: Friso M. de Beer, MD, Lieuwe D. J. Bos, PhD, Gerie J. Glas, MD, Roosmarijn T. M. van Hooijdonk, MD, Janneke Horn, MD, Laura R. A. Schouten, MD, Marleen Straat, MD, Marcus J. Schultz, MD, Luuk Wieske, MD, Esther Witteveen, MD. Center for Experimental and Molecular Medicine, Amsterdam University Medical Centers, location Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands: Arie J. Hoogendijk, PhD, Mischa A. Huson, MD, Tom van der Poll. MD, Brendon P. Scicluna, PhD, Lonneke A. van Vught, MD, Maryse A. Wiewel, MD.

Department of Medical Microbiology, Department of Intensive Care Medicine, and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; Peter M.C. Klein Klouwenberg, MD, David S.Y. Ong, MD; Department of Intensive Care Medicine and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; Jos F. Frencken, MD, Maria E. Koster-Brouwer, MSc, Kirsten van de Groep, MD, Diana M. Verboom, MD.

Funding

This work was supported by The Danish Heart Foundation, Denmark under grant no. R107-A6670; and Copenhagen University, Copenhagen, Denmark under grant no.: 373032.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101424.

References

[1] O.K.L. Helgestad, J. Josiassen, C. Hassager, et al., Temporal trends in incidence and patient characteristics in cardiogenic shock following acute myocardial infarction from 2010 to 2017: A Danish cohort study, Eur. J. Heart Fail. 21 (11) (Nov 2019) 1370–1378, https://doi.org/10.1002/ejhf.1566.

[2] J.S. Hochman, L.A. Sleeper, J.G. Webb, et al., Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock, N. Engl. J. Med. 341 (9) (1999) 625–634, https://doi.org/10.1056/NEJM199908263410901.

[3] H.R. Reynolds, J.S. Hochman, Cardiogenic shock: current concepts and improving outcomes, Circulation 117 (5) (2008) 686–697, https://doi.org/10.1161/CIRCULATIONAHA.106.613596.

[4] S. Kohsaka, V. Menon, K. Iwata, A. Lowe, L.A. Sleeper, J.S. Hochman, S. Investigators, Microbiological profile of septic complication in patients with cardiogenic shock following acute myocardial infarction (from the SHOCK study), Am. J. Cardiol. 99 (6) (2007) 802–804, https://doi.org/10.1016/j.amjcard.2006.10.040.

[5] S. Kohsaka, V. Menon, A.M. Lowe, et al., Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock, Arch. Intern. Med. 165 (14) (2005) 1643–1650, https://doi.org/10.1001/archinte.165.14.1643.

[6] J.C. Jentzer, P.R. Lawler, S. van Diepen, et al., Systemic inflammatory response syndrome is associated with increased mortality across the spectrum of shock severity in cardiac intensive care patients, Circ. Cardiovasc. Qual. Outcomes 13 (12) (Dec 2020) e006956.

[7] J.S. Hochman, Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm, Circulation 107 (24) (2003) 2998–3002, https://doi.org/10.1161/01.CIR.0000075927.67673.F2.

[8] S.M. Hollenberg, M. Singer, Pathophysiology of sepsis-induced cardiomyopathy, Nat. Rev. Cardiol. 18 (6) (Jun 2021) 424–434, https://doi.org/10.1038/s41569-020-00492-2.

[9] S.J. Beesley, G. Weber, T. Sarge, et al., Septic cardiomyopathy, Crit. Care Med. 46 (4) (Apr 2018) 625–634, https://doi.org/10.1097/CCM.0000000000002851.

[10] W.C. Aird, The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome, Blood 101 (10) (2003) 3765–3777, https://doi.org/10.1182/blood-2002-06-1887.

[11] K. Supel, M. Kacprzak, M. Zielinska, The prognostic value of MR-proadrenomedullin in patients with acute coronary syndrome complicated by cardiogenic shock, Biomarkers 22 (3–4) (May - Jun 2017) 296–303, https://doi.org/10.1080/1354750X.2016.1252962.

[12] H. Tomoda, Plasma endothelin-1 in acute myocardial infarction with heart failure, Am. Heart J. 125 (3) (Mar 1993) 667–672, https://doi.org/10.1016/0002-8703(93)90155-3.

[13] A. Kataja, T. Tarvasmaki, J. Lassus, et al., Kinetics of procalcitonin, C-reactive protein and interleukin-6 in cardiogenic shock - Insights from the CardShock study, Int. J. Cardiol. 322 (2021) 191–196, https://doi.org/10.1016/j.ijcard.2020.08.069.

[14] Theodorakopoulou MS, N.; Lignos, M.; Kandili, A.; Ioannidou, S.; Kavadia,E.; Armaganidis, A. C-reactive protein as a marker of septic shock and outcome in the intensive care unit. *Critical Care*. 2005;9(1):174. doi:10.1186/cc3237.

[15] L.A. van Vught, P.M. Klein Klouwenberg, C. Spitoni, et al., Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis, JAMA 315 (14) (2016) 1469–1479, https://doi.org/10.1001/jama.2016.2691.

[16] N.G. Morgenthaler, J. Struck, B. Thomas, A. Bergmann, Immunoluminometric assay for the midregion of pro-atrial natriuretic peptide in human plasma, Clin. Chem. 50 (1) (Jan 2004) 234–236, https://doi.org/10.1373/clinchem.2003.021204.

[17] J. Struck, C. Tao, N.G. Morgenthaler, A. Bergmann, Identification of an Adrenomedullin precursor fragment in plasma of sepsis patients, Peptides 25 (8) (Aug 2004) 1369–1372, https://doi.org/10.1016/j.peptides.2004.06.019.

[18] J. Struck, N.G. Morgenthaler, A. Bergmann, Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients, Peptides 26 (12) (Dec 2005) 2500–2504, https://doi.org/10.1016/j.peptides.2005.04.019.

[19] J. Papassotiriou, N.G. Morgenthaler, J. Struck, C. Alonso, A. Bergmann, Immunoluminometric assay for measurement of the C-terminal endothelin-1 precursor fragment in human plasma, Clin. Chem. 52 (6) (Jun 2006) 1144–1151, https://doi.org/10.1373/clinchem.2005.065581.

[20] J.L. Vincent, R. Moreno, J. Takala, et al., The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine, Intensive Care Med. 22 (7) (Jul 1996) 707–710, https://doi.org/10.1007/BF01709751.

[21] R. Doll, R. Peto, K. Wheatley, R. Gray, I. Sutherland, Mortality in relation to smoking: 40 years' observations on male British doctors, BMJ 309 (6959) (1994) 901–911, https://doi.org/10.1136/bmj.309.6959.901.

[22] Jortveit J, Halvorsen S, Kaldal A, Pripp AH, Govatsmark RES, Langorgen J. Unsatisfactory risk factor control and high rate of new cardiovascular events in patients with myocardial infarction and prior coronary artery disease. *BMC Cardiovasc Disord*. Mar 28 2019;19(1):71. doi:10.1186/s12872-019-1062-y.
[23] P. Lange, Chronic obstructive pulmonary disease and risk of infection, Pneumonol. Alergol. Pol. 77 (3) (2009) 284–288.
[24] Goto T, Yoshida K, Tsugawa Y, Filbin MR, Camargo CA, Jr., Hasegawa K. Mortality trends in U.S. adults with septic shock, 2005-2011: a serial cross-sectional analysis of nationally-representative data. *BMC Infect Dis*. Jun 14 2016;16:294. doi: 10.1186/s12879-016-1620-1.
[25] Vincent JL, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. *Crit Care*. May 31 2019;23(1):196. doi:10.1186/s13054-019-2478-6.
[26] M.M. Vis, R.J. VdS, K.D. Sjauw, et al., Creatinine clearance is independently associated with one year mortality in a primary PCI cohort with cardiogenic shock, Acute Card Care 11 (2) (2009) 107–112, https://doi.org/10.1080/17482940902915600.
[27] K. Kitamura, K. Kangawa, T. Eto, Adrenomedullin and PAMP: Discovery, structures, and cardiovascular functions, Microsc. Res. Tech. 57 (1) (2002) 3–13, https://doi.org/10.1002/jemt.10052.
[28] Wong HK, Cheung TT, Cheung BM. Adrenomedullin and cardiovascular diseases. *JRSM Cardiovasc Dis*. Aug 10 2012;1(5)doi:10.1258/cvd.2012.012003.
[29] S. Globits, H. Frank, B. Pacher, M. Huelsmann, E. Ogris, R. Pacher, Atrial natriuretic peptide release is more dependent on atrial filling volume than on filling pressure in chronic congestive heart failure, Am. Heart J. 135 (4) (Apr 1998) 592–597, https://doi.org/10.1016/s0002-8703(98)70272-8.
[30] I.A. Sergeeva, V.M. Christoffels, Regulation of expression of atrial and brain natriuretic peptide, biomarkers for heart development and disease, Biochim. Biophys. Acta 1832 (12) (Dec 2013) 2403–2413, https://doi.org/10.1016/j.bbadis.2013.07.003.
[31] N.G. Morgenthaler, J. Struck, C. Alonso, A. Bergmann, Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin, Clin. Chem. 52 (1) (Jan 2006) 112–119, https://doi.org/10.1373/clinchem.2005.060038.
[32] L. Buendgens, E. Yagmur, J. Bruensing, et al., C-terminal proendothelin-1 (CT-proET-1) is associated with organ failure and predicts mortality in critically ill patients, J. Intensive Care 5 (2017) 25, https://doi.org/10.1186/s40560-017-0219-y.
[33] Y. Hirata, C. Mitaka, K. Sato, T. Nagura, Y. Tsunoda, K. Amaha, F. Marumo, Increased circulating adrenomedullin, a novel vasodilatory peptide, in sepsis, J. Clin. Endocrinol. Metab. 81 (4) (Apr 1996) 1449–1453, https://doi.org/10.1210/jcem.81.4.8636349.
[34] Onal U, Valenzuela-Sanchez F, Vandana KE, Rello J. Mid-Regional Pro-Adrenomedullin (MR-proADM) as a Biomarker for Sepsis and Septic Shock: Narrative Review. *Healthcare (Basel)*. Sep 3 2018;6(3)doi:10.3390/healthcare6030110.
[35] Y. Hirata, H. Hayakawa, Y. Suzuki, et al., Mechanisms of adrenomedullin-induced vasodilation in the rat kidney, Hypertension 25 (4 Pt 2) (Apr 1995) 790–795, https://doi.org/10.1161/01.hyp.25.4.790.
[36] J. Josiassen, M. Frydland, L. Holmvang, et al., Mortality in cardiogenic shock is stronger associated to clinical factors than contemporary biomarkers reflecting neurohormonal stress and inflammatory activation, Biomarkers 25 (6) (Sep 2020) 506–512, https://doi.org/10.1080/1354750X.2020.1795265.
[37] M. Karakas, I. Akin, C. Burdelski, et al., Single-dose of adrecizumab versus placebo in acute cardiogenic shock (ACCOST-HH): an investigator-initiated, randomised, double-blinded, placebo-controlled, multicentre trial, Lancet Respir. Med. 10 (3) (Mar 2022) 247–254, https://doi.org/10.1016/S2213-2600(21)00439-2.
[38] Yagmur E, Sckaer JH, Koek GH, Weiskirchen R, Trautwein C, Koch A, Tacke F. Elevated MR-proANP plasma concentrations are associated with sepsis and predict mortality in critically ill patients. *J Transl Med*. Dec 12 2019;17(1):415. doi: 10.1186/s12967-019-02165-2.
[39] Ristagno G, Latini R, Plebani M, et al. Copeptin levels are associated with organ dysfunction and death in the intensive care unit after out-of-hospital cardiac arrest. *Crit Care*. Mar 31 2015;19:132. doi:10.1186/s13054-015-0831-y.
[40] M. Annborn, J. Dankiewicz, N. Nielsen, et al., CT-proAVP (copeptin), MR-proANP and Peroxiredoxin 4 after cardiac arrest: Release profiles and correlation to outcome, Acta Anaesthesiol. Scand. 58 (4) (Apr 2014) 428–436, https://doi.org/10.1111/aas.12282.
[41] N.G. Morgenthaler, B. Muller, J. Struck, A. Bergmann, H. Redl, M. Christ-Crain, Copeptin, a stable peptide of the arginine vasopressin precursor, is elevated in hemorrhagic and septic shock, Shock 28 (2) (Aug 2007) 219–226, https://doi.org/10.1097/SHK.0b013e318033e5da.
[42] Peters EJ, Berg ST, Bogerd M, et al. Characteristics, Treatment Strategies and Outcome in Cardiogenic Shock Complicating Acute Myocardial Infarction: A Contemporary Dutch Cohort. *J Clin Med*. Aug 10 2023;12(16)doi:10.3390/jcm12165221.
[43] L. Evans, A. Rhodes, W. Alhazzani, et al., Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021, Crit. Care Med. 49 (11) (2021) e1063–e1143, https://doi.org/10.1097/CCM.0000000000005337.
[44] Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. Aug 25 2023;doi:10.1093/eurheartj/ehad191.
[45] Naidu SS, Baran DA, Jentzer JC, et al. SCAI SHOCK Stage Classification Expert Consensus Update: A Review and Incorporation of Validation Studies: This statement was endorsed by the American College of Cardiology (ACC), American College of Emergency Physicians (ACEP), American Heart Association (AHA), European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC), International Society for Heart and Lung Transplantation (ISHLT), Society of Critical Care Medicine (SCCM), and Society of Thoracic Surgeons (STS) in December 2021. *J Am Coll Cardiol*. Mar 8 2022;79(9):933-946. doi:10.1016/j.jacc.2022.01.018.
[46] C. Adrie, M. Adib-Conquy, I. Laurent, et al., Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome, Circulation 106 (5) (2002) 562–568, https://doi.org/10.1161/01.cir.0000023891.80661.ad.