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► **To cite this version:**

Hamid Merdji, Anais Curtiaud, Antoine Aheto, Antoine Studer, Veli-Pekka Harjola, et al.. Performance of Early Capillary Refill Time Measurement on Outcomes in Cardiogenic Shock: An Observational, Prospective Multicentric Study. *American Journal of Respiratory and Critical Care Medicine*, 2022, 206 (10), pp.1230-1238. 10.1164/rccm.202204-0687OC . hal-03797275

**HAL Id: hal-03797275**

**<https://hal.univ-lorraine.fr/hal-03797275>**

Submitted on 4 Oct 2022

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# **Performance of early capillary refill time measurement on outcomes in cardiogenic shock. An observational, prospective multicentric study**

**Running title:** Microcirculation assessment in cardiogenic shock: The MicroShock study.

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**At a Glance:** This work provides new insights into the role of peripheral tissue perfusion signs such as capillary refill time in early cardiogenic shock. A prolonged capillary refill time > 3 sec was associated with an early prediction of 90-day outcome or the need for venoarterial extracorporeal membrane oxygenation support. Adding capillary refill time to CardShock risk score showed a marked improvement in CardShock prognostic properties with an area under the curve at 0.93.

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**Contributorship:**

- HM, HA and FM conceived the study
- HM, AC, AA, AS, AM, MK, BL, JH, AK, FM have been involved in the care of patients and hemodynamic assessment.
- HM, AC, AA and FM collected the data and wrote the manuscript.
- KD, NG and AK performed statistical analysis.
- AA, HA, BL, VH and AM participated in the revising of a manuscript.
- All authors approved the final manuscript.

**ACKNOWLEDGMENTS:** Many thanks to Dr. Thierry Boulain for his critical review and helpful comments on an earlier draft of the manuscript.

**Funding:** No funding.

**Descriptor number:** 4.5 Diagnostic Techniques & Monitoring

This article has an online data supplement, which is accessible from this issue's table of content online at [www.atsjournals.org](http://www.atsjournals.org).

## **Abstract**

*Background:* Identification of cardiogenic shock severity is a critical step to adapt the management level upon admission. Peripheral tissue perfusion signs, simple and reliable markers of tissue hypoperfusion have never been extensively assessed during cardiogenic shock.

*Methods:* All consecutive patients admitted in ICU for cardiogenic shock of two tertiary teaching hospitals were included in a prospective observational study. Macro-hemodynamic parameters (such as heart rate, blood pressure, left ventricular ejection fraction and cardiac index) and peripheral tissue perfusion signs such as capillary refill time on the index fingertip, mottling and Pv-aCO<sub>2</sub> (the difference between partial pressure of CO<sub>2</sub> in venous blood and arterial blood) were recorded at inclusion (H0), H6, H12, H24 and H48. The composite primary endpoint was the association between 90-day mortality or the need for venoarterial-ECMO support.

*Results:* 61 patients were included; at inclusion, simplified acute physiology score II was 64 (52–77) points. The primary endpoint was met by 42% of patients. Capillary refill time values were significantly higher at all time-points in non survivors or patients needing venoarterial-ECMO support. In univariate analysis, capillary refill time > 3 sec at inclusion was associated with 90-day all-cause mortality or venoarterial-ECMO support (Hazard Ratio of 12.38; 95% CI 2.91 to 52.71). Capillary refill time at inclusion was poorly associated with macrocirculatory parameters but significantly correlated with microcirculatory parameters. Further, capillary refill time added incremental value to Cardshock score, with an AUC combination at 0.93.

*Conclusion:* In patients admitted in ICU for cardiogenic shock, our preliminary data suggest that a prolonged capillary refill time > 3 sec was associated with an early prediction of 90-day mortality or the need for venoarterial-ECMO support.

**Abstract:** 272 words.

**Total words:** 3844 words.

**Key words:** Cardiogenic shock, heart failure, shock, microcirculation.

## **Introduction**

Cardiogenic shock (CS) is usually defined as a primary cardiac dysfunction with low cardiac output leading to critical organ hypoperfusion, tissue hypoxia (1, 2) and a high mortality rate (40%) despite recent advances (3). Mortality has mainly been associated with peripheral tissue perfusion signs disorders that extend beyond the macrocirculation and subsequently drive organ failure.

Many studies have now evidenced that CS not only involves perfusion abnormalities of the systemic macrocirculation, such as blood pressure (BP), left ventricular ejection fraction (LVEF) or cardiac index (4-7), but also involves significant uncorrelated abnormalities of the systemic microcirculation (8, 9). This terminal vascular network of the systemic circulation, formed by microvessels, arterioles, capillaries, and venules within organ tissues, is a terminal network, which main functions are oxygen and nutrient delivery, and carbon dioxide removal (10). It is also involved in regulating blood flow and tissue perfusion in response to cardiovascular alterations, in order to tailor oxygen delivery across microvascular beds with different oxygen needs.

Microcirculation can be directly visualized, using handheld microscopes, such as Orthogonally Polarized Spectral (OPS), Sidestream Dark-Field (SDF) or Incident Dark-Field (IDF) imaging techniques or tissue laser Doppler imaging (11), but with numerous limitations (12). Among them, the requirement of trained operators, limited availability of these different devices, lack of a clearly defined target value, difficult evaluation of the sublingual area in non-intubated patients and limited representativeness of microcirculatory impairment in other tissues (12).

Interestingly, traditional markers of peripheral tissue perfusion signs (capillary refill time (CRT), mottling,  $\Delta\text{PCO}_2$ ) were strongly linked with microcirculatory blood flow alteration during septic shock (13, 14). CRT measures the time required to recolor the tip of a finger.

Mottling is defined as patchy skin discoloration that usually starts around the knees. Central venous-arterial carbon dioxide difference ( $\Delta\text{PCO}_2$ ), also named Pv-aCO<sub>2</sub>, is the difference between partial pressure of CO<sub>2</sub> in venous blood and arterial blood (15).

Even if poor perfusion signs, such as cold extremities, mottling and elevated capillary refill time, are part of the various proposed definitions (16, 17) and are easy to assess, they have been poorly studied in CS to date (18). Indeed, no study has rigorously investigated them in CS.

The aim of this prospective observational study was to assess the correlation of CRT values with 90-day mortality in CS patients or the need for venoarterial extracorporeal membrane oxygenation (VA-ECMO) support. Other aims were to assess correlation between CRT and hemodynamic parameters using clinical parameters thoroughly validated in septic shock (19-22) and also to compare CRT contribution on CS survival (23).

## **Materials and methods**

### ***Study design and patients***

We conducted a prospective observational study in two tertiary teaching hospital, Strasbourg, and Nancy. During a 33-month period, between September 2018 and July 2021, all consecutive patients, older than 18 years, were included within the first 3 hours of admission in intensive care unit (ICU) for CS. However, due to the COVID-19 pandemic different waves, inclusions had to be temporarily stopped many times during successive waves. CS was defined according to the definition used in the 2016 FRENHOCK registry which considers all CS shock regardless of the etiology (see **Table S1 in the online data supplement**) (17). Thus, patients were included if they met at least one criterion of each of the following three components:

- low cardiac output, defined by systolic blood pressure < 90 mmHg and/or the need for amines (dobutamine and/or norepinephrine and/or epinephrine) to maintain systolic blood pressure > 90 mmHg and/or cardiac index < 2.2 L/min/m<sup>2</sup> on echocardiography or right heart catheterization;
- elevation of left and/or right heart pressures, defined by clinical signs, radiology (overload signs on chest X-ray or computed tomography scan), biological tests (natriuretic peptide elevation), echocardiography (usual signs of left ventricular filling pressure elevation) or invasive hemodynamic overload signs (elevation of mean pulmonary artery pressure or pulmonary capillary wedge pressure);
- signs of malperfusion, which could be clinical (oliguria, mottling, confusion) and/or biological (lactate > 2 mmol/L, hepatic insufficiency, renal failure).

In each case, an echocardiogram was performed to confirm the diagnosis. Patients were treated according to the most recent CS European and American guidelines at this time (24-26).

All patients had to be included within the first 3 hours of their admission. We excluded cardiac arrests, patients with dark skin as accurate clinical evaluation of perfusion signs such as mottling is difficult to assess, patients considered moribund by the attending physician and if non-opposition was not expressed by the patient or his/her relatives. Moribund status was defined according to a state of imminent death with no medical therapeutic option.

Approval was obtained from a regional ethics committee (*Comité de Protection des Personnes*, - CPP - Sud Est V; reference 18-STRA-01). All patients were informed through the informed non-opposition sheet about the study. In accordance with current French legislation, informed consent was not required for the prospective analysis of observational data routinely collected in the medical files. However, a non-opposition (considered as a tacit agreement) was mandatory. In unresponsive patients, informed non-opposition was first obtained from their closest relatives and thereafter in surviving patients who recovered consciousness.

### ***Outcome measures***

The primary composite outcome was to assess the association of CRT values with 90-day mortality or the need for VA-ECMO support in CS patients. Secondary outcomes were: the correlation between CRT and macrocirculatory parameters (such as heart rate, systolic blood pressure [SBP], cardiac index and cardiac power index [CPI]); the correlation between CRT and microcirculatory parameters (mottling, urinary output and  $\Delta\text{PCO}_2$ ); and the comparison between CRT with various scores (27) on 90-day mortality or VA-ECMO.

All clinical and paraclinical examinations were standardized and predefined in the protocol (clinicaltrials.gov; NCT03436641). Times of measurement were at inclusion (H0), H6, H12, H24 and H48.



General characteristics of the patients were recorded: demographic data, diagnoses, severity of illness evaluated by the sequential organ failure assessment (SOFA) score (within 6 hours of inclusion), with higher scores indicating a greater severity of organ dysfunction in critically ill patients (28) and simplified acute physiology score II (SAPS II) (29). Classification of CS was evaluated using the society of cardiovascular angiography and interventions (SCAI) cardiogenic shock stages (30), a system describing stages of CS from A to E. The CardShock risk score, consisting of seven common variables, was developed as a risk prediction tool for mortality in patients with CS (27). The vasoactive-inotropic score was also calculated. This score is used to quantify the amount of cardiovascular support the patient received by including weighted doses of dobutamine, epinephrine, milrinone, vasopressin, and norepinephrine (31).

At each time point, we collected data that reflected macrocirculation (hemodynamic measurements) and microcirculation (reflecting organ perfusion). Macrocirculation was assessed using invasive blood pressure monitoring (intra-arterial catheter), heart rate, left ventricular ejection fraction and cardiac index by echocardiography. Echocardiography parameters were assessed by physicians with adult echocardiography certification (32, 33) using the Vivid-S5 or S70 system (General Electric, Horton, Norway) with cardiac probe and with default cardiac imaging setting. Cardiac index ( $L/min/m^2$ ) were calculated by using standard formulae. Cardiac power index (CPI,  $W/m^2$ ) is the cardiac power output indexed to body surface area and were calculated as mean arterial pressure  $\times$  cardiac index/451 (34).

Microcirculatory dysfunction and organ perfusion were assessed through arterial lactate level, urinary output and clinical parameters reflecting perfusion signs obtained from the skin perfusion such CRT, skin mottling, central-to-toe temperature difference and  $\Delta PCO_2$ . CRT

procedure was *a priori* defined, and all investigators were trained with a video e-learning. CRT is the time for skin color to fully recover after applying a 15 sec firm pressure on the index finger (35). The pressure applied was just enough to remove the blood at the tip of the physician's nail illustrated by appearance of a thin white distal crescent (blanching) under the nail. The time for return of the normal skin color was registered with a chronometer, and by analogy with other shock state etiologies, a refill time greater than 3 seconds was defined as abnormal (20, 36). To reduce measurements variability, it was recommended to average three successive measures of CRT. Mottling of the anterior aspect of the knee was assessed visually on both legs. Patients were placed supine with the legs straight and at the level of the heart. Mottling score which describes the extent of the mottled area on the knee and thigh was determined on a 6-point scale ranging from 0 to 5 as described previously (19). If mottling was present, then the leg with more prominent mottling was chosen for scoring. Mottling score is an easy-to-learn and easy-to-use score with excellent inter-rater reproducibility, recorded routinely for several years in Strasbourg and Nancy ICU. Central to peripheral temperature difference was the difference between central temperature measured by a bladder thermistor catheter and peripheral temperature measured by a skin probe on the big toe of the foot (27).  $\Delta\text{PCO}_2$ , also named  $\text{PCO}_2$  gap or  $\text{Pv-aCO}_2$ , was calculated by subtracting arterial blood ( $\text{PaCO}_2$ ) to partial pressure of  $\text{CO}_2$  in superior vena cava blood ( $\text{PvCO}_2$ ) measured on arterial and central venous samples taken simultaneously.

### ***Statistical analysis***

Analytical data are presented as the median with 25<sup>th</sup> and 75<sup>th</sup> percentiles (median (interquartile range)) for continuous variables, whereas categorical variables as numbers and percentages. Comparisons of baseline characteristics according to groups were conducted by using Mann–Whitney for continuous variables and the Fisher exact test or  $\chi^2$  test for

categorical variables. Mann–Whitney test was used to assess between groups difference for repeated measures at each time. A post-hoc Benjamini-Hochberg correction was performed to adjust p-values. Univariate Cox proportional-hazards regression were used to analyze the association of CRT at H0 according to its usual threshold (3 sec) or by tercile of CRT at H0 with 90-day mortality or VA-ECMO support. Schoenfeld test was performed to assess the proportional hazard assumption. For illustration, a survival curve was drawn according to the usual threshold value of CRT at H0 (3 sec) and by tercile of CRT at H0 by using the Kaplan-Meier method. Spearman test was used to test correlations. ROC curves were drawn, and AUC were provided. Comparison between AUC values were performed using the Delong test. The ROC curve was used to identify the optimal threshold using the ‘closest to topleft’ method, *i.e.* the threshold that minimizes the criterion  $(1 - \text{Sensitivity})^2 + (1 - \text{Specificity})^2$ . This cut-off was used to evaluate the sensitivity, specificity, negative predictive value and positive predictive values. Confidence intervals were calculated from on 2,000 stratified bootstrap samples. The prognostic value of CRT at H0 in category ( $\leq 3$  sec;  $> 3$  sec) on top of CardShock score for 90-day mortality or VA-ECMO support was assessed using continuous net reclassification improvement (cNRI) and increase in area under the curve (AUC). A two-sided p-value  $\leq 0.05$  was regarded as statistically significant. Statistical analyses were performed using R, version 4.1.1 (2021-08-10) (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### *Study population at inclusion (H0)*

During the prespecified prospective inclusion period, 61 consecutive patients were included and because of missing CRT at inclusion (H0) for two patients, 59 were analyzed. Baseline characteristics are summarized in **Table 1**. CS criteria used to define CS in the study population are reported in **Table S1**. Primary cause of CS was ischemic in 31%. The median age of the study population was 71 years (65 - 78) and 51% were men. Median LVEF was 25 % (20 - 39) and median cardiac index was 1.80 L/min/m<sup>2</sup> (1.30 - 2.10). The prevalence of the SCAI cardiogenic shock stages were as follows: A: 0%; B: 3%; C: 39%; D: 31%; and E: 27%. The median SOFA score measured 6 hours after admission was 8 (7 - 10) points and the median SAPS II was 64 (52 - 77) points. The median vasoactive-inotropic score was 30 (5 - 69) and 85% were treated with mechanical ventilation. Characteristics of the population according to CRT are presented in **Table 1**. Briefly, patients with a CRT > 3 sec compared to patients with CRT ≤ 3 sec had no difference in demographic characteristics and medical history except for coronary artery disease (CRT ≤ 3 sec: 25% vs CRT > 3 sec: 57%  $p=0.015$ ). Baseline characteristics of the patients with acute myocardial infarction cardiogenic shock (AMICS) are summarized in **Table S2**. Overall death at 90 days occurred in 39% of the patients with an HR: 10.59 (95% CI 2.48 - 45.30) for patients with CRT > 3 sec (**see Figure S1 in the online data supplement**).

### *Time course and primary endpoint: association between CRT and 90-day mortality or need for VA-ECMO support*

Twenty-five patients (42%) met the composite primary endpoint. At day 90, 23 patients had died, and 4 patients had been placed on VA-ECMO (of which two had died within 90 days)

(**Figure 1**). CRT values were higher in 90-day non-survivors at day 90 and patients who received VA-ECMO than in survivors at all predefined time-points (**Figure 2**).

**Figure S2, S3 and S4** show the relative comparison of CRT and lactate over time, the time course of lactate and associations between lactate and microcirculatory parameters. **Figure 3** shows an association between a CRT > 3 sec at H0 and 90-day mortality or VA-ECMO with a HR: 12.38 (95% CI: 2.91 – 52.71). **Figure S5** confirms the predefined CRT threshold of 3 sec at H0 with an association which occurred from the second tercile of CRT (CRT ]3 sec - 4.2 sec], HR: 13.90 [95% CI: 3.14 – 61.44]). **Figure S6** highlights the risk of not normalizing the CRT within the first six hours after H0 with a HR: 6.32 (95% CI: 2.36 – 16.96).

### *Secondary endpoints*

#### *Association between CRT at H0 and circulatory parameters*

There were no associations between CRT and bedside macrocirculatory parameters such as SBP, heart rate, CPI, and cardiac index (**Figure S7**). Conversely, CRT at H0 was associated with microcirculatory parameters (**Figure 4**). Briefly, CRT was significantly shorter in patients with a mottling score of 0 (2.49 sec [2.00 - 3.00]) than in patients with a mottling score of 1-2 (4 sec [3.10 - 6.70]) or a mottling score of 3-4-5 (4.70 sec [4.00 - 7.00]),  $p=0.0001$ ). CRT at H0 was also correlated with the arterial lactate level ( $R=0.36$ ,  $p=0.006$ ) and the  $\Delta\text{PCO}_2$  ( $R=0.34$ ,  $p=0.017$ ) all collected at H0. Finally, during the first 24 hours, diuresis was higher in patients presenting less occurrence of CRT > 3 sec, 0 to 1 occurrence: 1.24 ml/kg/h [0.71 - 1.82] versus 2-3-4 occurrences: 0.64 ml/kg/h ([0.09 - 1.61],  $p= 0.048$ ) (**Figure 4**).

Central to peripheral temperature difference was correlated to CRT at H6 (**Figure S8**) and was similar between survivors and 90-day non-survivors or VA-ECMO at all predefined time-points (**Figure S9**).

***Comparison between CRT at H0 and different parameters or validated scores in CS on 90-day survival or VA-ECMO***

AUC for CRT at H0 to predict 90-day mortality or VA-ECMO support was similar to other scores *i.e.* SAPS2, lactate at H6, or CardShock risk score (**Figure 5**). With a best threshold at 3.05 sec (95% CI: 3.05 – 4.10), CRT in continuous had a specificity of 0.71 (95% CI: 0.50 – 0.88) and a sensitivity of 0.92 (95% CI: 0.68 – 1.00). With a 90-day mortality or VA-ECMO support prevalence at 42%, the positive predictive value was 0.69 (95% CI: 0.58 – 0.83) and the negative predictive value was 0.91 (95% CI: 0.78 – 1.00). Finally, the combination of CardShock score with CRT categorized according to the 3 sec thresholds resulted in a greater performance to predict 90-day mortality or VA-ECMO support than CardShock score alone (**Figure 5**), improving the AUC from 0.810 (95% CI: 0.70 – 0.91) to 0.93 (95% CI: 0.86 – 1.00) and continuous NRI: 113.4 (74.90 – 151.90).

## **Discussion**

Prediction of CS survival on admission is a challenge, requiring the use of complex clinical symptoms and biomarkers while managing a critical hemodynamic situation. In this prospective observational study of CS patients, we assessed the impact of a simple standardized CRT on 90-day survival or need for VA-ECMO support. The main result of this prospective study in patients with CS is that CRT was systematically prolonged at all time points in patients with a poor outcome and the best cut-off was, as in septic shock, 3 seconds. Importantly, CRT was not associated with macrocirculatory hemodynamic parameters, but was strongly associated with microcirculatory parameters.

While the literature is largely focused on acute myocardial infarction-induced CS, only 43 % of the patients had an acute coronary syndrome in our study. Consequently, our study contributes to a more contemporary description of the CS population, as it was done recently in the largest CS survey to date where ischemic trigger accounted for only 36.3% of patients, even if was still the first cause of CS (37). The overall short-term mortality is 39% in the present study, which is in line with the mortality rate in recent major studies on cardiogenic shock (27, 38-40). In addition, short-term mortality according to each SCAI shock stage was also similar to the biggest SCAI SHOCK stage validation study (41).

Restoration of microcirculation hemodynamic parameters is the primary goal in the management of CS. Although international guidelines recommend continuous BP monitoring in CS, there is currently no international consensus for guidance and monitoring of hemodynamic support in patients with CS (42). To date, evidence-based therapies available in CS patients remain limited, and much of the strategies have been extrapolated from other non-CS populations (26, 43). While some guidelines advise the use of inotropes in CS patients with SBP < 90 mmHg (42), some guidelines suggest target of MAP  $\geq$  65 mmHg in all circulatory shock states including CS (44). However, none of these BP targets has been

validated in randomized clinical trials to date (45). A recent retrospective study provides indirect support for a MAP target of 65 mmHg assessing an increased risk of mortality in patients with a MAP below 65 mmHg during the first 24h after ICU admission for CS (46). Despite progress in the management of CS, by promptly restoring hemodynamics, mortality remains unacceptably high. This significant mortality is partly due to profound alterations of microcirculatory blood flow during CS, leading to multi organ failure (6, 8, 9), despite restoration of macro-hemodynamic parameters such as BP and cardiac output.

In a recent sub study of the IABP-SHOCK II trial, that was the first randomized study directly investigating the microcirculation in CS, Jung *et al.* assessed perfused capillary densities (< 20  $\mu\text{m}$ ), perfused vessel densities (< 100  $\mu\text{m}$ ), total capillary densities and total vessel densities using a SDF intravital microscope (6). Results revealed no difference regarding these microcirculation parameters between patients treated with or without intra-aortic balloon pump (IABP). This inability to improve microcirculation may partly explains the lack of benefit of the IABP in CS (47). Although controversial,  $\Delta\text{PCO}_2$  was assessed as a microcirculatory parameter since Ospina-Tascon (15), and others (48), has well highlighted the good correlation between  $\Delta\text{PCO}_2$  and microvascular blood flow during the early phases of septic shock.

Even if imaging monitoring tools have revealed that microcirculatory disorders may persist despite the apparent normalization of macrohemodynamic parameters, these tools have several limitations as mentioned previously (12, 49). Fortunately, at the bedside, CRT and mottling are “easy to use, easy to learn” clinical manifestations of microperfusion disorders in circulatory shock states (13, 18). In 2014, a task force of the European Society of Intensive Care Medicine (ESICM) recommended assessing abnormal skin perfusion in their consensus on circulatory shock and hemodynamic monitoring (44). Moreover, these simple tools may even prove interesting to guide hemodynamic management in CS. A recent large, randomized



control clinical trial, the ANDROMEDA-SHOCK trial, suggested that CRT can be used to guide early resuscitation in septic shock (36). A Bayesian reanalysis of this study even shown that peripheral perfusion-targeted resuscitation may result in lower mortality and faster resolution of organ dysfunction when compared with a lactate-targeted resuscitation strategy (50).

The main finding of this study is that a simple parameter such as the CRT may markedly predict 90-day mortality or VA-ECMO support in CS. Combination of CRT with CardShock risk score, which has already a good performance in predicting short-term mortality in CS (27), showed a marked predicting improvement with an AUC at 0.932. CRT and other peripheral tissue perfusion signs may also be integrated with other variables to develop practical tools for risk assessment of short-term mortality for patients with CS, such as the SAVE score (51), to help clinicians in their decision-making processes for VA-ECMO indications (52). Thus, further prospective research is warranted to confirm how using physiology and physiological responsiveness for precision medicine could be integrated in cardiogenic shock management (53).

**Limitations.** We performed a prospective observational study on patients with CS, and exclusion criteria were very limited to reflect “real life”. However, several limitations of this study need to be acknowledged. First, even if the size of this preliminary study was not very large, it was enough to highlight significant results. In addition, our results are in line with numerous studies investigating microcirculation in CS (5-9), and with studies investigating clinical signs of peripheral hypoperfusion in septic shock (19-21, 54). One explanation for the low inclusion rate is the COVID-19 pandemic, the eastern region of France being the most severely affected (55). Another explanation is that the inclusion time frame was very short to perform the first measurements, which was within the first 3 hours after the diagnostic of CS,

thus excluding many patients transferred from peripheral centers. Secondly, by contrast with the ANDROMEDA-SHOCK trial (36) in septic shock, we did not assess CRT using a glass microscope slide. Instead, we used a simple finger pressure technique already validated with good reproducibility and excellent interrater concordance (20). Fully automated device capable of performing CRT measurements now exists and could facilitate its standardization and routine use (56). Third, our findings were not validated on an external cohort. However, to the best of our knowledge, there is no CS cohort assessing repeatedly clinical parameters of peripheral hypoperfusion such as the CRT,  $\Delta\text{PCO}_2$  or the central-to-toe temperature difference. Interestingly, the FRENHOCK prospective study reported that mottling at admission for CS was significantly associated with 30-day mortality (37). Fourth, dark skin patients were not included only because accurate clinical evaluation of mottling is difficult to assess in this population. However, in this dark skin population, CRT on the index fingertip or  $\Delta\text{PCO}_2$  could be interesting options and reliable parameters to assess perfusion signs. Finally, due to the sample size limitation, a multivariate analysis would have been overfitted. However, CRT at H0, when  $\leq 3\text{s}$ , is almost constantly associated with a good outcome and thus its predictive value is more deterministic than probabilistic.

## **Conclusion**

In this prospective multicenter observational study of critically ill patients with cardiogenic shock, our preliminary data suggest that CRT was systematically prolonged at all assessed time points in patients with a poor outcome. Importantly, CRT was not correlated with macro-hemodynamic parameters but was correlated with microcirculatory-measured parameters. CRT is a simple noninvasive, priceless tool allowing a real time assessment of microcirculation at bedside, which seems to be strongly associated with the outcome. Further prospective research is warranted to confirm this finding and to delineate the most efficient way to integrate it in early CS management.

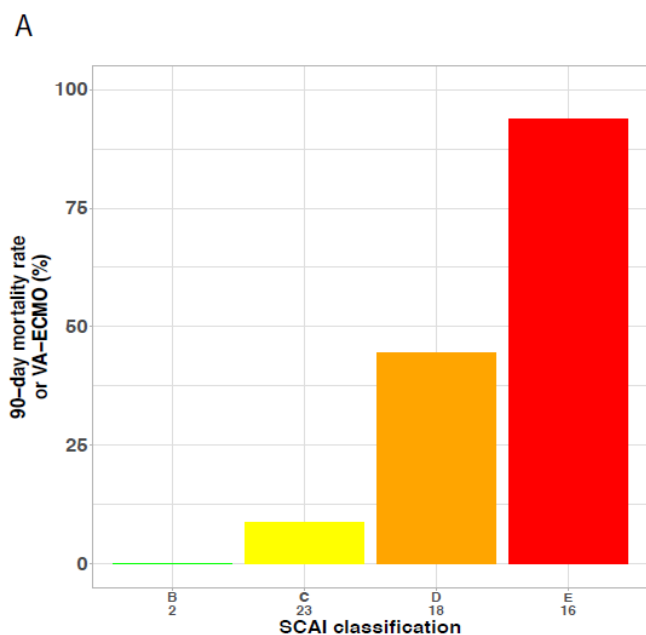
Table 1: Description of the total ICU population at inclusion and according to capillary refill time measured at inclusion

Variable	n	Total population	n	CRT $\leq$ 3sec	n	CRT> 3sec	p
<i>Demographic</i>							
Age (years)	59	71 (65 - 78)	24	70 (59 - 77)	35	71 (66 - 80)	0.25
Male gender (%)	59	30 (51 %)	24	11 (46 %)	35	19 (54 %)	0.52
BMI (kg/m <sup>2</sup> )	59	27 (23 - 30)	24	27 (24 - 34)	35	27 (22 - 30)	0.27
<i>Medical history</i>							
Hypertension (%)	59	38 (64 %)	24	16 (67 %)	35	22 (63 %)	0.76
Diabetes mellitus (%)	59	24 (41 %)	24	9 (38 %)	35	15 (43 %)	0.68
Smoking (%)	36	8 (22 %)	13	2 (15 %)	23	6 (26 %)	0.68
Coronary artery disease (%)	59	26 (44 %)	24	6 (25 %)	35	20 (57 %)	0.015
<i>Clinical presentation</i>							
Heart rate (bpm)	59	83 (70 - 120)	24	79 (70 - 108)	35	93 (75 - 125)	0.55
Systolic arterial pressure (mmHg)	59	100 (85 - 122)	24	110 (88 - 128)	35	96 (82 - 120)	0.099
Diastolic arterial pressure (mmHg)	59	61 (50 - 67)	24	64 (50 - 72)	35	59 (47 - 65)	0.16
Mean arterial pressure (mmHg)	59	72 (62 - 80)	24	73 (64 - 90)	35	70 (58 - 76)	0.081
Cardiac index (l/min/m <sup>2</sup> )	55	1.8 (1.3 - 2.1)	22	1.7 (1.3 - 2.1)	33	1.8 (1.4 - 2.1)	0.97
Cardiac power index (W/m <sup>2</sup> )	55	0.3 (0.2 - 0.3)	22	0.3 (0.2 - 0.3)	33	0.3 (0.2 - 0.3)	0.69
LVEF (%)	56	25 (20 - 39)	22	34 (22 - 40)	34	20 (15 - 38)	0.021
Ischemic cause (%)	59	18 (31 %)	24	9 (38 %)	35	9 (26 %)	0.33
Lactate (mmol/l)	55	3.2 (1.7 - 6.3)	22	2.1 (1.5 - 5.2)	33	3.7 (2.1 - 8.3)	0.020
<i>SCAI SHOCK CLASSIFICATION</i>							
B		2 (3 %)		2 (8 %)		0 (0 %)	
C		23 (39 %)		12 (50 %)		11 (31 %)	
D		18 (31 %)		8 (33 %)		10 (29 %)	
E		16 (27 %)		2 (8 %)		14 (40 %)	
<i>Severity scores</i>							
SAPS II score	58	64 (52 - 77)	23	60 (44 - 64)	35	68 (58 - 80)	0.011
SOFA score	51	8 (7 - 10)	21	7 (6 - 10)	30	9 (7 - 11)	0.16
<i>Management</i>							
VIS	59	30 (5 - 69)	24	13 (0 - 42)	35	48 (5 - 90)	0.030
Mechanical ventilation (%)	59	50 (85 %)	24	20 (83 %)	35	30 (86 %)	1.00
RRT (%)	59	17 (29 %)	24	5 (21 %)	35	12 (34 %)	0.26
<i>Outcomes</i>							
Length of stay in ICU (days)	59	4 (2 - 8)	24	6 (4 - 8)	35	3 (2 - 8)	0.039
90-day non-survivor (%)	59	23 (39 %)	24	2 (8 %)	35	21 (60 %)	<0.0001
VA-ECMO (%)	59	4 (7 %)	24	0 (0 %)	35	4 (11 %)	0.14
90-day non-survivor or VA-ECMO (%)	59	25 (42 %)	24	2 (8 %)	35	23 (66 %)	<0.0001

## Tables and figures

Table 1: Baseline Characteristics of the Study Population.

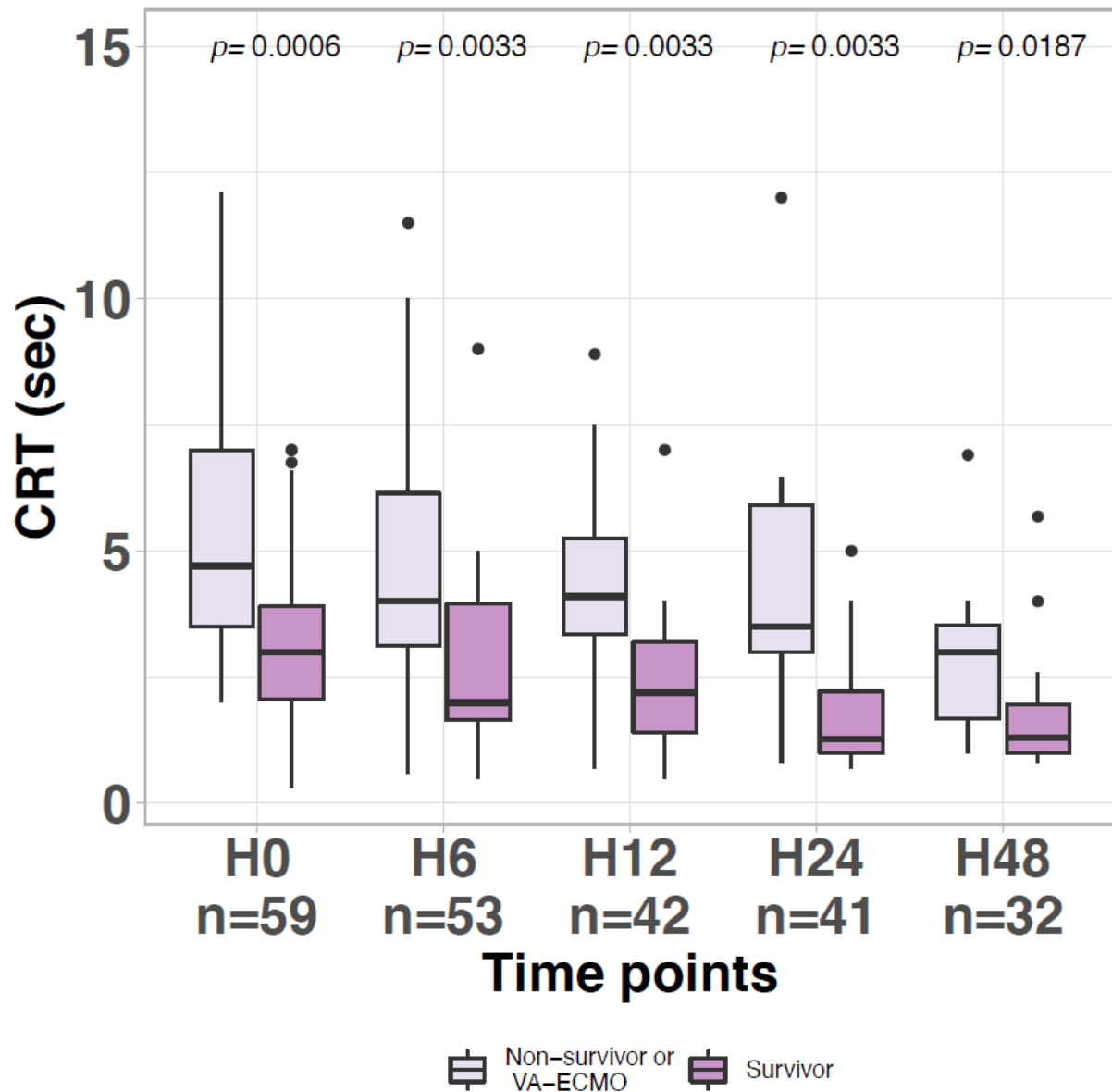
Categorical variables are expressed as absolute counts (%) and continuous variables as median (25th to 75th percentile). BMI = body mass index; LVEF = left ventricular ejection fraction; SAPS = simplified acute physiology score; SOFA = sequential organ failure assessment; VIS = vasoactive-inotropic score; ICU = intensive care unit; ECMO = extracorporeal membrane oxygenation.



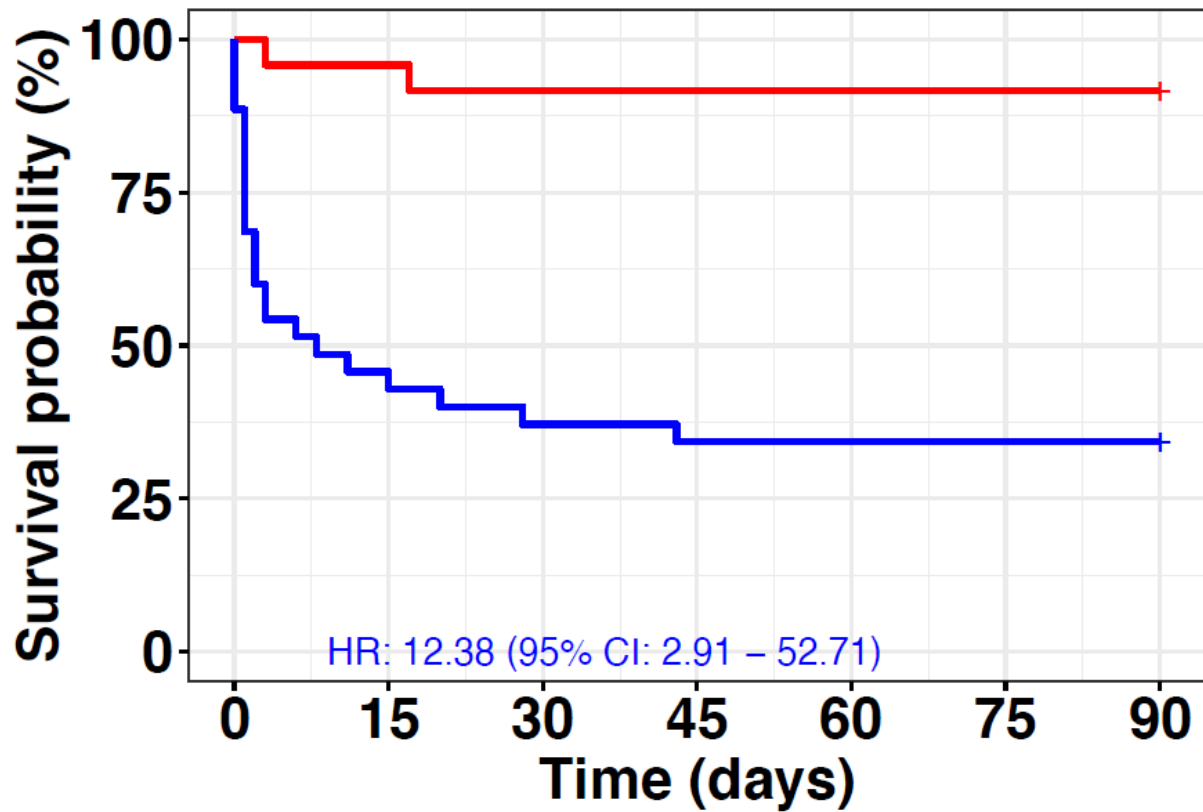
**B**  
Contingency table of CRT threshold at 3 sec according to 90-day status or VA-ECMO and SCAI classification

SCAI	status	n CRT $\leq$ 3 sec	CRT $\leq$ 3 sec %	n CRT >3 sec	CRT >3 sec %	p
E	survivor	1	100.0	0	0.0	0.1250
E	non-survivor or VA-ECMO	1	6.7	14	93.3	
D	survivor	7	70.0	3	30.0	0.0248
D	non-survivor or VA-ECMO	1	12.5	7	87.5	
C	survivor	12	57.1	9	42.9	0.2170
C	non-survivor or VA-ECMO	0	0.0	2	100.0	
B	survivor	2	100.0	0	0.0	
B	non-survivor or VA-ECMO	0	0.0	0	0.0	

**Figure 1: Panel A: 90-day mortality or VA-ECMO support according to SCAI classification. Panel B: Contingency table of CRT threshold at 3 sec according to 90-day status or VA-ECMO support and SCAI classification.**



**Figure 2: Time-course comparison of CRT at inclusion (H0) and H6, H12, H24 and H48, between 90-day survivors and 90-day non survivors or VA-ECMO (p values adjusted).**



Number at risk

$CRT \leq 3s$	24	23	22	22	22	22	22
$CRT > 3s$	35	16	13	12	12	12	12
	0	15	30	45	60	75	90

**Figure 3: Kaplan–Meier curves for 90-day mortality or VA-ECMO in patients with CRT > 3 sec vs. CRT ≤ 3 sec at H0.**

HR, hazard ratio.

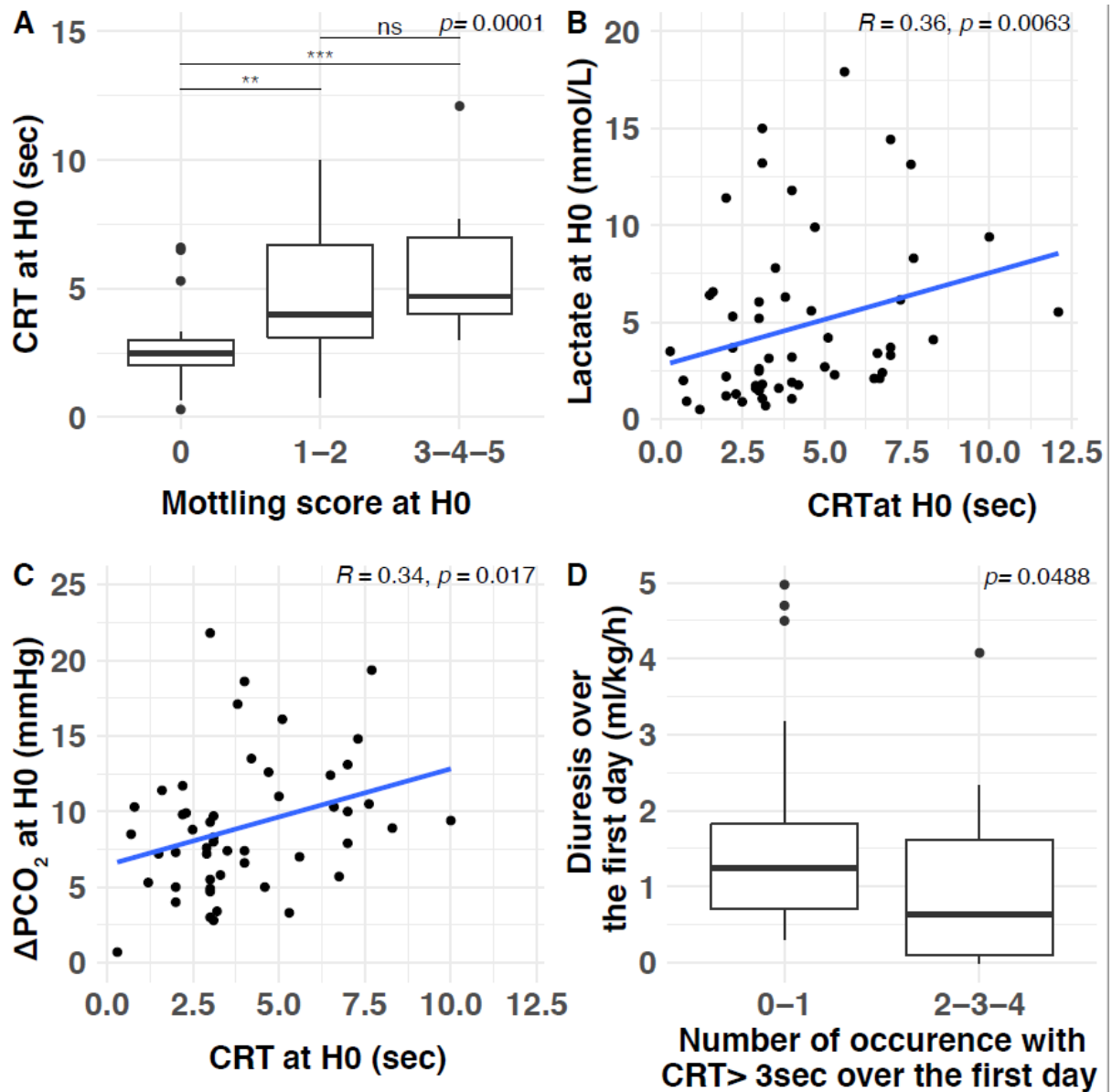
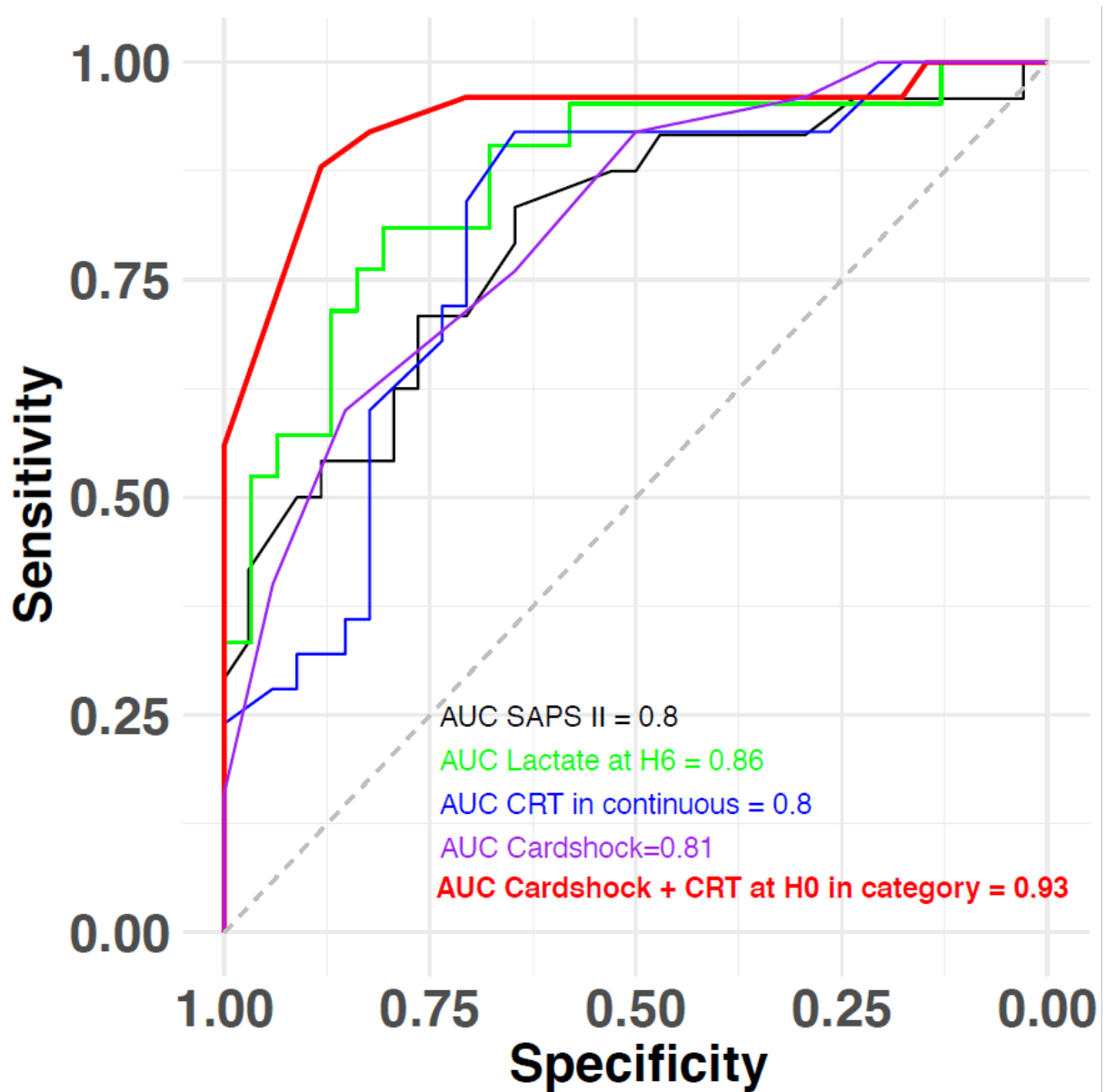


Figure 4: Comparisons of CRT at H0 and microcirculatory parameters. Panel A: Association of CRT at H0 with categories of mottling score at H0 (p values adjusted), Panel B: correlation between lactate at H0 and CRT at H0, Panel C: Correlation between  $\Delta PCO_2$  and CRT at H0, Panel D: Association of diuresis over the first day and the number of time CRT is > 3 sec over the first day.





**Figure 5: ROC curves of SAPS II, lactate at H6, CRT (continuous value), Cardshock score and Cardshock score plus CRT threshold (3 sec) according to 90-day mortality or VA-ECMO.**

## References

1. Reventovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. *Nat Rev Cardiol* 2016; 13: 481-492.
2. Tehrani BN, Truesdell AG, Psotka MA, Rosner C, Singh R, Sinha SS, Damluji AA, Batchelor WB. A Standardized and Comprehensive Approach to the Management of Cardiogenic Shock. *JACC Heart Fail* 2020; 8: 879-891.
3. Arrigo M, Jessup M, Mullens W, Reza N, Shah AM, Sliwa K, Mebazaa A. Acute heart failure. *Nat Rev Dis Primers* 2020; 6: 16.
4. De Backer D, Ortiz JA, Salgado D. Coupling microcirculation to systemic hemodynamics. *Curr Opin Crit Care* 2010; 16: 250-254.
5. den Uil CA, Lagrand WK, van der Ent M, Jewbali LS, Cheng JM, Spronk PE, Simoons ML. Impaired microcirculation predicts poor outcome of patients with acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J* 2010; 31: 3032-3039.
6. Jung C, Fuernau G, de Waha S, Eitel I, Desch S, Schuler G, Figulla HR, Thiele H. Intraaortic balloon counterpulsation and microcirculation in cardiogenic shock complicating myocardial infarction: an IABP-SHOCK II substudy. *Clin Res Cardiol* 2015; 104: 679-687.
7. Wijntjens GW, Fengler K, Fuernau G, Jung C, den Uil C, Akin S, van de Hoef TP, Serpytis R, Diletti R, Henriques JP, Serpytis P, Thiele H, Piek JJ. Prognostic implications of microcirculatory perfusion versus macrocirculatory perfusion in cardiogenic shock: a CULPRIT-SHOCK substudy. *Eur Heart J Acute Cardiovasc Care* 2020; 9: 108-119.
8. De Backer D, Creteur J, Dubois MJ, Sakr Y, Vincent JL. Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. *Am Heart J* 2004; 147: 91-99.
9. Jung C, Ferrari M, Rodiger C, Fritzenwanger M, Goebel B, Lauten A, Pfeifer R, Figulla HR. Evaluation of the sublingual microcirculation in cardiogenic shock. *Clin Hemorheol Microcirc* 2009; 42: 141-148.
10. Guven G, Hilty MP, Ince C. Microcirculation: Physiology, Pathophysiology, and Clinical Application. *Blood Purif* 2020; 49: 143-150.
11. Mongkolpun W, Orbegozo D, Cordeiro CPR, Franco C, Vincent JL, Creteur J. Alterations in Skin Blood Flow at the Fingertip Are Related to Mortality in Patients With Circulatory Shock. *Crit Care Med* 2020; 48: 443-450.
12. De Backer D. Is microcirculatory assessment ready for regular use in clinical practice? *Curr Opin Crit Care* 2019; 25: 280-284.
13. Hariri G, Joffre J, Leblanc G, Bonsey M, Laviellegrand JR, Urbina T, Guidet B, Maury E, Bakker J, Ait-Oufella H. Narrative review: clinical assessment of peripheral tissue perfusion in septic shock. *Ann Intensive Care* 2019; 9: 37.
14. Ait-Oufella H, Bakker J. Understanding clinical signs of poor tissue perfusion during septic shock. *Intensive Care Med* 2016; 42: 2070-2072.
15. Ospina-Tascon GA, Umana M, Bermudez WF, Bautista-Rincon DF, Valencia JD, Madrinan HJ, Hernandez G, Bruhn A, Arango-Davila C, De Backer D. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? *Intensive Care Med* 2016; 42: 211-221.
16. Jones TL, Nakamura K, McCabe JM. Cardiogenic shock: evolving definitions and future directions in management. *Open Heart* 2019; 6: e000960.
17. Delmas C, Puymirat E, Leurent G, Elbaz M, Manzo-Silberman S, Bonello L, Gerbaud E, Bataille V, Levy B, Lamblin N, Bonnefoy E, Henry P, Roubille F, investigators F.

- Design and preliminary results of FRENDSHOCK 2016: A prospective nationwide multicentre registry on cardiogenic shock. *Arch Cardiovasc Dis* 2019; 112: 343-353.
18. Jung C. Assessment of microcirculation in cardiogenic shock. *Curr Opin Crit Care* 2019; 25: 410-416.
  19. Ait-Oufella H, Lemoinne S, Boelle PY, Galbois A, Baudel JL, Lemant J, Joffre J, Margetis D, Guidet B, Maury E, Offenstadt G. Mottling score predicts survival in septic shock. *Intensive Care Med* 2011; 37: 801-807.
  20. Ait-Oufella H, Bige N, Boelle PY, Pichereau C, Alves M, Bertinchamp R, Baudel JL, Galbois A, Maury E, Guidet B. Capillary refill time exploration during septic shock. *Intensive Care Med* 2014; 40: 958-964.
  21. Bourcier S, Pichereau C, Boelle PY, Nemlaghi S, Dubee V, Lejour G, Baudel JL, Galbois A, Lavillegrand JR, Bige N, Tahiri J, Leblanc G, Maury E, Guidet B, Ait-Oufella H. Toe-to-room temperature gradient correlates with tissue perfusion and predicts outcome in selected critically ill patients with severe infections. *Ann Intensive Care* 2016; 6: 63.
  22. Gattinoni L, Vasques F, Camporota L, Meessen J, Romitti F, Pasticci I, Duscio E, Vassalli F, Forni LG, Payen D, Cressoni M, Zanella A, Latini R, Quintel M, Marini JJ. Understanding Lactatemia in Human Sepsis. Potential Impact for Early Management. *Am J Respir Crit Care Med* 2019; 200: 582-589.
  23. Kalra S, Ranard LS, Memon S, Rao P, Garan AR, Masoumi A, O'Neill W, Kapur NK, Karmaliotis D, Fried JA, Burkhoff D. Risk Prediction in Cardiogenic Shock: Current State of Knowledge, Challenges and Opportunities. *J Card Fail* 2021; 27: 1099-1110.
  24. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, Ristic AD, Lambrinou E, Masip J, Riley JP, McDonagh T, Mueller C, deFilippi C, Harjola VP, Thiele H, Piepoli MF, Metra M, Maggioni A, McMurray J, Dickstein K, Damman K, Seferovic PM, Ruschitzka F, Leite-Moreira AF, Bellou A, Anker SD, Filippatos G. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail* 2015; 17: 544-558.
  25. Mebazaa A, Tolppanen H, Mueller C, Lassus J, DiSomma S, Bakshyte G, Cecconi M, Choi DJ, Cohen Solal A, Christ M, Masip J, Arrigo M, Nouira S, Ojji D, Peacock F, Richards M, Sato N, Sliwa K, Spinar J, Thiele H, Yilmaz MB, Januzzi J. Acute heart failure and cardiogenic shock: a multidisciplinary practical guidance. *Intensive Care Med* 2016; 42: 147-163.
  26. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG, American Heart Association Council on Clinical C, Council on C, Stroke N, Council on Quality of C, Outcomes R, Mission L. Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation* 2017; 136: e232-e268.
  27. Harjola VP, Lassus J, Sionis A, Kober L, Tarvasmaki T, Spinar J, Parissis J, Banaszewski M, Silva-Cardoso J, Carubelli V, Di Somma S, Tolppanen H, Zeymer U, Thiele H, Nieminen MS, Mebazaa A, CardShock Study I, network G. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail* 2015; 17: 501-509.
  28. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG. 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* 1996; 22: 707-710.
29. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; 270: 2957-2963.
  30. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, Hollenberg SM, Kapur NK, O'Neill W, Ornato JP, Stelling K, Thiele H, van Diepen S, Naidu SS. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv* 2019; 94: 29-37.
  31. Belletti A, Lerose CC, Zangrillo A, Landoni G. Vasoactive-Inotropic Score: Evolution, Clinical Utility, and Pitfalls. *J Cardiothorac Vasc Anesth* 2021; 35: 3067-3077.
  32. Expert Round Table on Echocardiography in ICU. International consensus statement on training standards for advanced critical care echocardiography. *Intensive Care Med* 2014; 40: 654-666.
  33. Wiegers SE, Ryan T, Arrighi JA, Brown SM, Canaday B, Damp JB, Diaz-Gomez JL, Figueredo VM, Garcia MJ, Gillam LD, Griffin BP, Kirkpatrick JN, Klarich KW, Lui GK, Maffett S, Naqvi TZ, Patel AR, Poulin MF, Rose GA, Swaminathan M. 2019 ACC/AHA/ASE advanced training statement on echocardiography (revision of the 2003 ACC/AHA clinical competence statement on echocardiography): A Report of the ACC Competency Management Committee. *Catheter Cardiovasc Interv* 2019; 94: 481-505.
  34. Fincke R, Hochman JS, Lowe AM, Menon V, Slater JN, Webb JG, LeJemtel TH, Cotter G, Investigators S. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. *J Am Coll Cardiol* 2004; 44: 340-348.
  35. Schriger DL, Baraff L. Defining normal capillary refill: variation with age, sex, and temperature. *Ann Emerg Med* 1988; 17: 932-935.
  36. Hernandez G, Ospina-Tascon GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, Friedman G, Castro R, Alegria L, Teboul JL, Cecconi M, Ferri G, Jibaja M, Pairumani R, Fernandez P, Barahona D, Granda-Luna V, Cavalcanti AB, Bakker J, The ASI, the Latin America Intensive Care N, Hernandez G, Ospina-Tascon G, Petri Damiani L, Estenssoro E, Dubin A, Hurtado J, Friedman G, Castro R, Alegria L, Teboul JL, Cecconi M, Cecconi M, Ferri G, Jibaja M, Pairumani R, Fernandez P, Barahona D, Cavalcanti AB, Bakker J, Hernandez G, Alegria L, Ferri G, Rodriguez N, Holger P, Soto N, Pozo M, Bakker J, Cook D, Vincent JL, Rhodes A, Kavanagh BP, Dellinger P, Rietdijk W, Carpio D, Pavez N, Henriquez E, Bravo S, Valenzuela ED, Vera M, Dreyse J, Oviedo V, Cid MA, Larroulet M, Petruska E, Sarabia C, Gallardo D, Sanchez JE, Gonzalez H, Arancibia JM, Munoz A, Ramirez G, Aravena F, Aquevedo A, Zambrano F, Bozinovic M, Valle F, Ramirez M, Rossel V, Munoz P, Ceballos C, Esveile C, Carmona C, Candia E, Mendoza D, Sanchez A, Ponce D, Ponce D, Lastra J, Nahuelpan B, Fasce F, Luengo C, Medel N, Cortes C, Campassi L, Rubatto P, Horna N, Furche M, Pendino JC, Bettini L, Lovesio C, Gonzalez MC, Rodruguez J, Canales H, Caminos F, Galletti C, Minoldo E, Aramburu MJ, Olmos D, Nin N, Tenzi J, Quiroga C, Lacuesta P, Gaudin A, Pais R, Silvestre A, Olivera G, Rieppi G, Berrutti D, Ochoa M, Cobos P, Vintimilla F, Ramirez V, Tobar M, Garcia F, Picoita F, Remache N, Granda V, Paredes F, Barzallo E, Garces P, Guerrero F, Salazar S, Torres G, Tana C, Calahorrano J, Solis F, Torres P, Herrera L, Ornes A, Perez V, Delgado G,

- Lopez A, Espinosa E, Moreira J, Salcedo B, Villacres I, Suing J, Lopez M, Gomez L, Toctaquiza G, Cadena Zapata M, Orazabal MA, Pardo Espejo R, Jimenez J, Calderon A, Paredes G, Barberan JL, Moya T, Atehortua H, Sabogal R, Ortiz G, Lara A, Sanchez F, Hernan Portilla A, Davila H, Mora JA, Calderon LE, Alvarez I, Escobar E, Bejarano A, Bustamante LA, Aldana JL. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. *JAMA* 2019; 321: 654-664.
37. Delmas C, Roubille F, Lamblin N, Bonello L, Leurent G, Levy B, Elbaz M, Danchin N, Champion S, Lim P, Schneider F, Cariou A, Khachab H, Bourenne J, Seronde MF, Schurtz G, Harbaoui B, Vanzetto G, Quentin C, Delabranche X, Aissaoui N, Combaret N, Manzo-Silberman S, Tomasevic D, Marchandot B, Lattuca B, Henry P, Gerbaud E, Bonnefoy E, Puymirat E. Baseline characteristics, management, and predictors of early mortality in cardiogenic shock: insights from the FRENDSHOCK registry. *ESC Heart Fail* 2022; 9: 408-419.
  38. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Bohm M, Ebelt H, Schneider S, Schuler G, Werdan K, Investigators I-SIT. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012; 367: 1287-1296.
  39. Berg DD, Bohula EA, van Diepen S, Katz JN, Alviar CL, Baird-Zars VM, Barnett CF, Barsness GW, Burke JA, Cremer PC, Cruz J, Daniels LB, DeFilippis AP, Haleem A, Hollenberg SM, Horowitz JM, Keller N, Kontos MC, Lawler PR, Menon V, Metkus TS, Ng J, Orgel R, Overgaard CB, Park JG, Phreaner N, Roswell RO, Schulman SP, Jeffrey Snell R, Solomon MA, Ternus B, Tymchak W, Vikram F, Morrow DA. Epidemiology of Shock in Contemporary Cardiac Intensive Care Units. *Circ Cardiovasc Qual Outcomes* 2019; 12: e005618.
  40. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, Nordbeck P, Geisler T, Landmesser U, Skurk C, Fach A, Lapp H, Piek JJ, Noc M, Goslar T, Felix SB, Maier LS, Stepinska J, Oldroyd K, Serpytis P, Montalescot G, Barthelemy O, Huber K, Windecker S, Savonitto S, Torremante P, Vrints C, Schneider S, Desch S, Zeymer U, Investigators C-S. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. *N Engl J Med* 2017; 377: 2419-2432.
  41. Jentzer JC, van Diepen S, Barsness GW, Henry TD, Menon V, Rihal CS, Naidu SS, Baran DA. Cardiogenic Shock Classification to Predict Mortality in the Cardiac Intensive Care Unit. *J Am Coll Cardiol* 2019; 74: 2117-2128.
  42. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, Group ESCSD. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; 42: 3599-3726.
  43. Gershengorn HB, Stelfox HT, Niven DJ, Wunsch H. Association of Premorbid Blood Pressure with Vasopressor Infusion Duration in Patients with Shock. *Am J Respir Crit Care Med* 2020; 202: 91-99.
  44. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL, Rhodes A. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med* 2014; 40: 1795-1815.

45. Mathew R, Fernando SM, Hu K, Parlow S, Santo PD, Brodie D, Hibbert B. Optimal Perfusion Targets in Cardiogenic Shock. *JACC: Advances* 2022; 1: 1-14.
46. Burstein B, Tabi M, Barsness GW, Bell MR, Kashani K, Jentzer JC. Association between mean arterial pressure during the first 24 hours and hospital mortality in patients with cardiogenic shock. *Crit Care* 2020; 24: 513.
47. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, de Waha A, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Lauer B, Bohm M, Ebel H, Schneider S, Werdan K, Schuler G, Intraaortic Balloon Pump in cardiogenic shock Iiti. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet* 2013; 382: 1638-1645.
48. Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL. Sublingual capnometry tracks microcirculatory changes in septic patients. *Intensive Care Med* 2006; 32: 516-523.
49. Ince C, Boerma EC, Cecconi M, De Backer D, Shapiro NI, Duranteau J, Pinsky MR, Artigas A, Teboul JL, Reiss IKM, Aldecoa C, Hutchings SD, Donati A, Maggiorini M, Taccone FS, Hernandez G, Payen D, Tibboel D, Martin DS, Zarbock A, Monnet X, Dubin A, Bakker J, Vincent JL, Scheeren TWL, Cardiovascular Dynamics Section of the E. Second consensus on the assessment of sublingual microcirculation in critically ill patients: results from a task force of the European Society of Intensive Care Medicine. *Intensive Care Med* 2018; 44: 281-299.
50. Zampieri FG, Damiani LP, Bakker J, Ospina-Tascon GA, Castro R, Cavalcanti AB, Hernandez G. Effects of a Resuscitation Strategy Targeting Peripheral Perfusion Status versus Serum Lactate Levels among Patients with Septic Shock. A Bayesian Reanalysis of the ANDROMEDA-SHOCK Trial. *Am J Respir Crit Care Med* 2020; 201: 423-429.
51. Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, Hodgson C, Scheinkestel C, Cooper DJ, Thiagarajan RR, Brodie D, Pellegrino V, Pilcher D. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J* 2015; 36: 2246-2256.
52. Ventetuolo CE, Muratore CS. Extracorporeal life support in critically ill adults. *Am J Respir Crit Care Med* 2014; 190: 497-508.
53. Goligher EC, Talias I, Sahetya SK, Baedorf-Kassis E, Patel BK, Yehya N, Silversides JA, Ferguson ND, Brochard LJ, Lawler PR, Zarychanski R, Slutsky AS. Physiology Is Vital to Precision Medicine in Acute Respiratory Distress Syndrome and Sepsis. *Am J Respir Crit Care Med* 2022; 206: 14-16.
54. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002; 166: 98-104.
55. Salje H, Tran Kiem C, Lefrancq N, Courtejoie N, Bosetti P, Paireau J, Andronico A, Hoze N, Richet J, Dubost CL, Le Strat Y, Lessler J, Levy-Bruhl D, Fontanet A, Opatowski L, Boelle PY, Cauchemez S. Estimating the burden of SARS-CoV-2 in France. *Science* 2020; 369: 208-211.
56. Blaxter LL, Morris DE, Crowe JA, Henry C, Hill S, Sharkey D, Vyas H, Hayes-Gill BR. An automated quasi-continuous capillary refill timing device. *Physiol Meas* 2016; 37: 83-99.