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Original Contribution

# Skin mottling score and capillary refill time to assess mortality of septic shock since pre-hospital setting☆

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ABSTRACT

*Objectives:* The early identification of septic shock patients at high risk of poor outcome is essential to early initiate optimal treatments and to decide on hospital admission. Biomarkers are often used to evaluate the severity. In prehospital settings, the availability of biomarkers, such as lactate, is restricted. In this context, clinical tools such as skin mottling score (SMS) and capillary refill time (CRT) are more suitable.

In this study, we describe prehospital SMS and CRT's ability to predict mortality of patients with septic shock initially cared in the prehospital setting by a mobile intensive care unit.

*Methods:* Patients with septic shock who received prehospital medical care admitted to the intensive care unit were retrospectively analyzed.

*Results:* Sixty-three patients were included. The origin of sepsis was mainly pulmonary (67%). Overall mortality reached 36%. No significant difference was observed in the duration of prehospital medical care between alive and deceased patients. Mean prehospital value of SMS was $3 \pm 2$ and mean prehospital value of CRT was $5 \pm 1$ s. A significant association was found between mortality and prehospital SMS ($p = 0.02$, OR[CI95] = 1.50 [1.08–2.15]) and prehospital CRT ($p = 0.04$, OR[CI95] = 1.53 [1.04–2.37]).

After adjusting for confounding factors using propensity score, the relative risk of death was 6.58 for SMS > 2 and 2.03 for CRT > 4 s.

*Conclusion:* In this study, we report an association between prehospital SMS and CRT, and mortality of patients with septic shock. SMS and CRT are simple tools that could be used to optimize the triage and to decide early intensive care admission.



## 1. Introduction

Septic shock affects approximately 19 million people worldwide annually [1, 2] and results in 180,000 deaths in the United States of America [3]. Septic shock is responsible for one-third to one-half of all in-hospital deaths [4]. The Centres for Disease Control and Prevention and the "sepsis 3" conference [5] underlined the early recognition and treatment of sepsis as priorities to improve the survival rate. Actually, the outcome relies on the early identification of patients at high risk of poor outcome, their orientation to the most appropriate ward, i.e. emergency department (ED) or intensive care unit (ICU), and thus the rapid implementation of appropriate treatments, including hemodynamic optimization and antibiotics administration [3, 6].

In the physiopathology of septic shock both the macro- and the microcirculation are altered. Despite differences between systemic hemodynamic parameters and vascular capillaries, evaluation of the microcirculation through clinical examination of the skin is often

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used to assess the severity of the sepsis [6]. Additionally, dysfunction of the microcirculation was suggested to better predict patients' outcome [7-9].

The guidelines of the surviving sepsis campaign [10] recommended the evaluation of tissue perfusion after initial fluid resuscitation to fulfil the bundle of care, through repeated assessment of vital signs, cardio-pulmonary function, pulse, capillary refill time (CRT) and Skin mottling score (SMS). Central venous pressure measurement, central venous oxygen saturation measurement, bedside cardiovascular ultrasound or dynamic assessment of fluid responsiveness through passive leg raising or fluid challenge also remains of interest [10]. Contrasting with the in-hospital environment, in the pre-hospital setting, biomarkers availability is restricted, reinforcing the interest for clinical tools.

SMS and CRT are clinical tools that reflect the microcirculation and can thus be used as indicators of reduced peripheral perfusion [11, 12] impacting on the prognosis of patients. SMS is defined as irregular patchy cutaneous discoloration area mainly observed on the knee [13, 14], whereas CRT is the time taken for the blood flow to reach distal capillaries after pressure applied onto the skin to cause blanching is released [12]. Both signs are simple to collect at physical examination. SMS [14, 15] and CRT [13, 16-18], correlated with the severity of sepsis, underlying their potential prognosis value [13, 14, 19, 20].

The aim of this study was to describe SMS and CRT ability to assess mortality at day 28 of patients with septic shock initially cared for in prehospital setting by a mobile intensive care unit.

## 2. Methods

### 2.1. Study population

All consecutive patients with septic shock receiving prehospital medical care by a mobile intensive care unit (MICU) between January

**Table 1**
Demographic characteristics of patients with septic shock cared for by a prehospital mobile intensive care unit.
Initial variables were collected in the prehospital setting at first medical contact and finial variables at ICU admission. Quantitative variables are expressed as mean ± standard deviation (SD). Qualitative variables are expressed as absolute value and percentage

| Quantitative covariates | Alive ($n = 41$) | Deceased ($n = 22$) | Overall ($n = 63$) |
|---|---|---|---|
| Age (years) | 71 ± 14 | 73 ± 13 | 71 ± 14 |
| Weight (kg) | 69 ± 10 | 67 ± 15 | 68 ± 12 |
| Size (cm) | 170 ± 8 | 169 ± 8 | 170 ± 8 |
| Initial value | | | |
| SBP (mm Hg) | 97 ± 35 | 95 ± 35 | 96 ± 35 |
| DBP (mm Hg) | 57 ± 24 | 57 ± 26 | 57 ± 25 |
| MBP (mm Hg) | 69 ± 26 | 69 ± 28 | 69 ± 26 |
| HR (bpm) | 115 ± 29 | 102 ± 38 | 110 ± 33 |
| RR (mpm) | 30 ± 9 | 33 ± 9 | 31 ± 9 |
| Pulse oximetry (%) | 87 ± 13 | 83 ± 14 | 85 ± 13.2 |
| Temperature (°C) | 37.3 ± 2.6 | 37.8 ± 1.8 | 37.5 ± 2.3 |
| Blood glucose (mmol/l) | 11.2 ± 6.8 | 9.3 ± 6.2 | 10.5 ± 6.6 |
| Glasgow coma scale | 13 ± 3 | 12 ± 4 | 12 ± 3 |
| SMS | 3 ± 2 | 4 ± 1 | 3.2 ± 2 |
| CRT | 4 ± 1 | 5 ± 1 | 5 ± 1 |
| Fluid volume expansion (ml) | 1188 ± 617 | 938 ± 474 | 1099 ± 579 |
| Norepinephrine dose (mg.h$^{-1}$) | 1.2 ± 0.9 | 1.0 ± 0.6 | 1.14 ± 0.78 |
| Final value | | | |
| SBP (mm Hg) | 107 ± 28 | 87 ± 26 | 100 ± 29 |
| DBP (mm Hg) | 60 ± 19 | 49 ± 16 | 56 ± 19 |
| MBP (mm Hg) | 75 ± 20 | 62 ± 18 | 71 ± 20 |
| HR (bpm) | 108 ± 24 | 103 ± 36 | 106 ± 28 |
| RR (mpm) | 36 ± 8 | 30 ± 11 | 28 ± 9 |
| Pulse oximetry (%) | 96 ± 7 | 93 ± 20 | 94 ± 13 |
| Temperature (°C) | 37.2 ± 2.7 | 37.3 ± 2.2 | 37.2 ± 2.5 |
| Blood glucose (mmol/l) | 10.9 ± 6.7 | 10.2 ± 5.5 | 10.7 ± 6.2 |
| Glasgow coma scale | 14 ± 2 | 13 ± 4 | 13 ± 3 |
| SMS | 3 ± 2 | 4 ± 1 | 3 ± 2 |
| CRT (sec) | 5 ± 1 | 5 ± 2 | 5 ± 2 |
| SMS shift (h$^{-1}$) | −0.05 ± 1.32 | −0.05 ± 0.77 | −0.05 ± 1.15 |
| CRT shift (sec·h$^{-1}$) | −0.01 ± 1.0 | −0.04 ± 1.4 | −0.3 ± 1.3 |
| Prehospital duration (min) | 88 ± 32 | 90 ± 35 | 85 ± 33 |
| ICU length of stay (days) | 10 ± 6 | 7 ± 6 | 9 ± 6 |
| IGS2 | 66 ± 16 | 82 ± 18 | 72 ± 18 |
| SOFA score | 9 ± 3 | 13 ± 4 | 10 ± 4 |
| **Qualitative covariates** | | | |
| Female gender | 11 (27%) | 9 (41%) | 21 (33%) |
| HBP history | 19 (46%) | 13 (59%) | 33 (52%) |
| Coronaropathy | 5 (12%) | 4 (18%) | 9 (14%) |
| Cardiac insufficiency | 2 (5%) | 3 (14%) | 5 (8%) |
| Chronic kidney disease | 5 (12%) | 3 (14%) | 8 (13%) |
| Diabetes | 14 (34%) | 6 (27%) | 20 (32%) |
| COPD | 4 (9%) | 2 (9%) | 6 (10%) |
| Cancer | 12 (29%) | 5 (22%) | 17 (27%) |
| Immunosuppression | 11 (27%) | 7 (32%) | 18 (29%) |
| Chronic alcoholism | 14 (33%) | 2 (9%) | 16 (25%) |
| HIV | 1 (2%) | 2 (9%) | 3 (4%) |

Legend: SBP = systolic blood pressure (mmHg), DBP = diastolic blood pressure (mmHg), MBP = mean blood pressure (mmHg), RR = respiratory rate (movement per minute), HR = heart rate (beats per minute), SMS = skin mottling score, CRT = capillary refill time (sec), ICU = intensive care unit, IGS=Index Gravity Score, SOFA = Sequential Organ Failure Assessment, HBP = high blood pressure, COPD = Chronic Obstructive Pulmonary Disease and HIV = human immunodeficiency virus.

2016 and December 2017 in Paris - Ile de France area (France), were retrospectively included. Septic shock was defined according to the surviving sepsis campaign criteria [8].

As previously described [21], in France, out-of-hospital emergencies are managed by the Service d'Aide Médicale Urgente (SAMU), the name for pre-hospital emergency service [22]. For medical assistance, the SAMU is reached dialling the national number "15". The SAMU hospital-based team is composed of switchboard operators and physicians. Over the phone, the SAMU physician determines the appropriate level of care to dispatch to the scene, based on the patient's symptoms communicated by the patient himself, by relatives or any witness. For life-threatening emergencies, the "Service Mobile d'Urgence et de Réanimation" (SMUR) dispatches to the scene a MICU to initiate treatments. The MICU team is composed of a driver, a nurse and an emergency physician [22].

In keeping with the French legislation, our local ethical committee (Comité de Protection des Personnes, Ile de France, Paris) considered that consent of patients was waived for participation in this observational study (Number: 2015-08-03-SC).

### 2.2. Data collection

Variables were defined prior to data collection and included patients' demographic characteristics (age, weight, size, and gender), immunosuppression status, prehospital vital signs (mean blood pressure, diastolic and systolic blood pressure, heart rate, pulse oximetry, respiratory rate, and temperature), skin mottling score (from 0 to 5), capillary refill time (in seconds), duration of prehospital care, length of stay in the ICU, Sequential Organ Failure Assessment (SOFA) score and mortality at day 28. Sequential Organ Failure Assessment (SOFA) score was calculated 24 h after ICU admission [23].

Mortality at day 28 was retrieved from hospital medical reports.

Immunosuppression was defined by the presence of one or more of the following elements: diabetes mellitus, chronic renal insufficiency, and infection by human immunodeficiency virus.

Data for SMS and CRT were extracted from the MICU prehospital medical reports.

A SMS chart was used to determine the SMS score. SMS was scored from 0 to 5, with 0 defined as no mottling and 5 as severe mottling extending beyond the groin [13, 14]. CRT was assessed with a watch timer. CRT was evaluated in seconds.

SMS and CRT were assessed in the prehospital setting by the MICU physician establishing the initial values and then by the ICU physician establishing the final value.

SMS and CRT shift were calculated using prehospital and ICU values standardized by the duration of prehospital care, according to the following formulae:

$$Shift = (Initial\ value - Final\ value)\ /\ Prehospital\ setting\ duration\ (hour)$$

In order to minimize the bias in data abstraction [24], data collection was performed by a single investigator using a standardized abstraction template.

### 2.3. Statistical analysis

SMS was quoted as an absolute value or percentage in each category according to the following classification: 0–1, 2–3 and 4–5, as previously reported [14]. For statistical analyses, a threshold for abnormal values of SMS > 2 [14] and CRT > 4 s [16, 18, 25] were considered, according to previous studies.

Univariate and multivariable analyses were conducted to evaluate the relationship between all covariates and mortality at day 28.

A propensity score analysis was performed to reduce the effect of confounders [26]. Covariates considered as potentially interfering with the decision on ICU admission were included in the propensity score. Imbalance matching was assessed with standardized mean deviation, as described by Austin [27]. The formulae used to determine the standardized mean deviation (SMD) was:

$$SMD = 100 * \frac{|\,x\ (cases) - x\ (controls)\,|}{\sqrt{(s\ cases)^2 + s\ (controls)^2}}$$

where x denotes the mean or proportion for binary variables and classes of categorical variables et s the variance.

In the matched sample, baseline characteristics included in the propensity score were compared between cases and controls by paired tests. All $p$ values were two-tailed and $p < 0.05$ was considered significant. As $p$ value is influenced by the sample size, standardized mean deviation was used for statistical testing.

To study the predictive value of SMS > 2 for mortality at day 28, the covariates included in propensity score were age, length of stay in ICU, and immunosuppression. For CRT > 4, the covariates included in the propensity score were age, body temperature, length of stay in ICU and systolic blood pressure.

At least, to estimate the average treatment effect, relative risk (RR) for mortality at day 28 was evaluated for SMS > 2 and CRT > 4.

Results are expressed as mean with standard deviation for quantitative gaussian parameters and, as absolute value and percentage for qualitative parameters. Results are given as Odds Ratio (OR) with 95% confidence interval [CI95].

All analyses were performed using R 3.4.2 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

### 3.1. Study characteristics

Sixty-three patients with septic shock initially cared for septic shock in the prehospital setting prior to their admission in the ICU were included in this study.

Populations' demographic and clinical characteristics are summarized in Table 1. Forty-two patients (67%) were male. The mean age was 71 ± 14 years. Septic shock was mainly associated with pulmonary (67%), abdominal (17%) or urinary (10%) infection (Table 2). The mean length of stay in the ICU was of 9 ± 6 days (Table 1). Overall mortality reached 36% at day 28.

### 3.2. Main measurements

No significant difference was observed in the duration of prehospital medical care between alive and deceased patients (88 ± 32 min vs 90 ± 35 min respectively, $p = 0.35$; Table 1). Mean prehospital fluid expansion reached 1099 ± 579 ml in the overall population and was not significantly different between alive and deceased patients (1188 ± 617 ml vs 938 ± 474 ml respectively, $p = 0.09$) (Table 1). Twenty-seven (43%) patients received

**Table 2**
Origin of sepsis of patients with septic shock initially cared for by a prehospital mobile intensive care unit.
Data are expressed as absolute value with percentage.

| Site of infection | n (%) |
|---|---|
| Pulmonary | 42 (67%) |
| Digestive | 11 (17%) |
| Urinary | 7 (10%) |
| Cutaneous | 1 (2%) |
| Meningeal | 1 (2%) |
| Undefined | 1 (2%) |

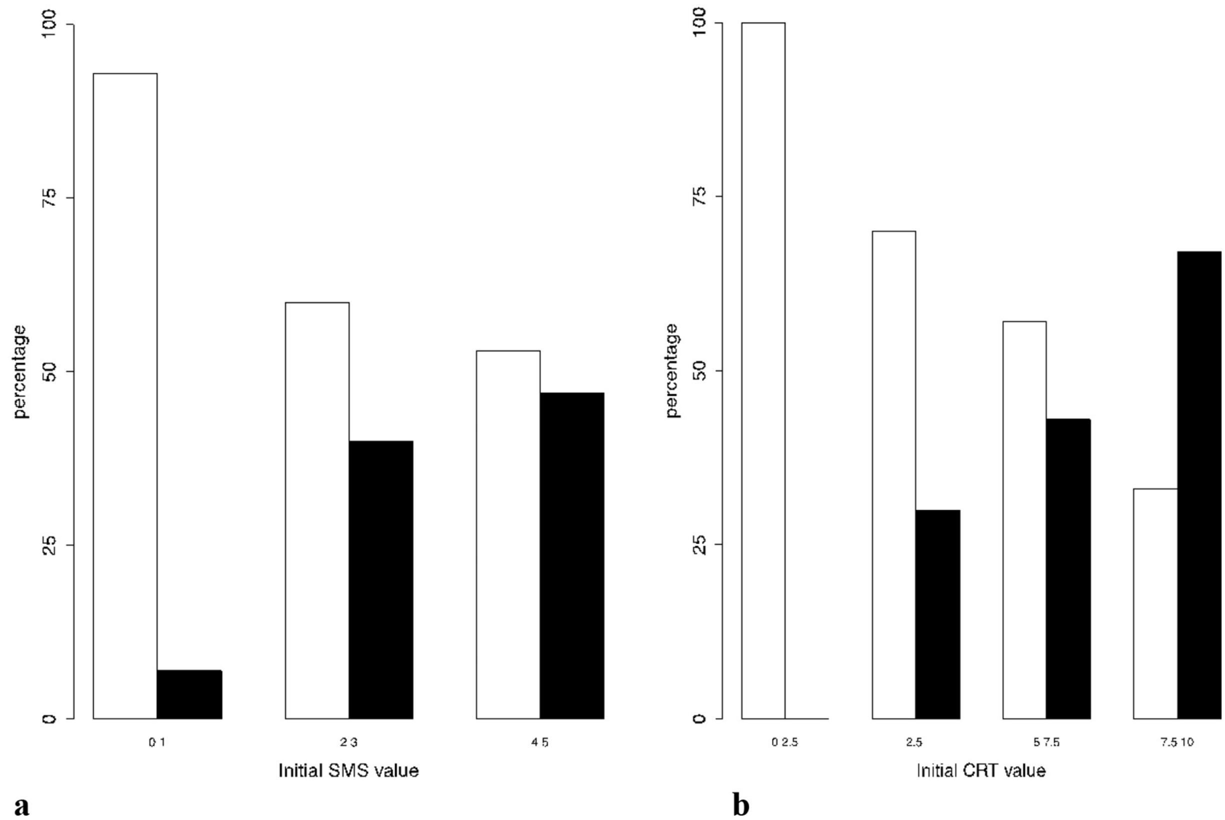


**Fig. 1.** Deceased and alive patients at day 28 in the predefined categories of prehospital skin mottling score (1a) and capillary refill time (1b). Results are given as percentage. White plots represent alive patients, and black plots represent deceased patients.

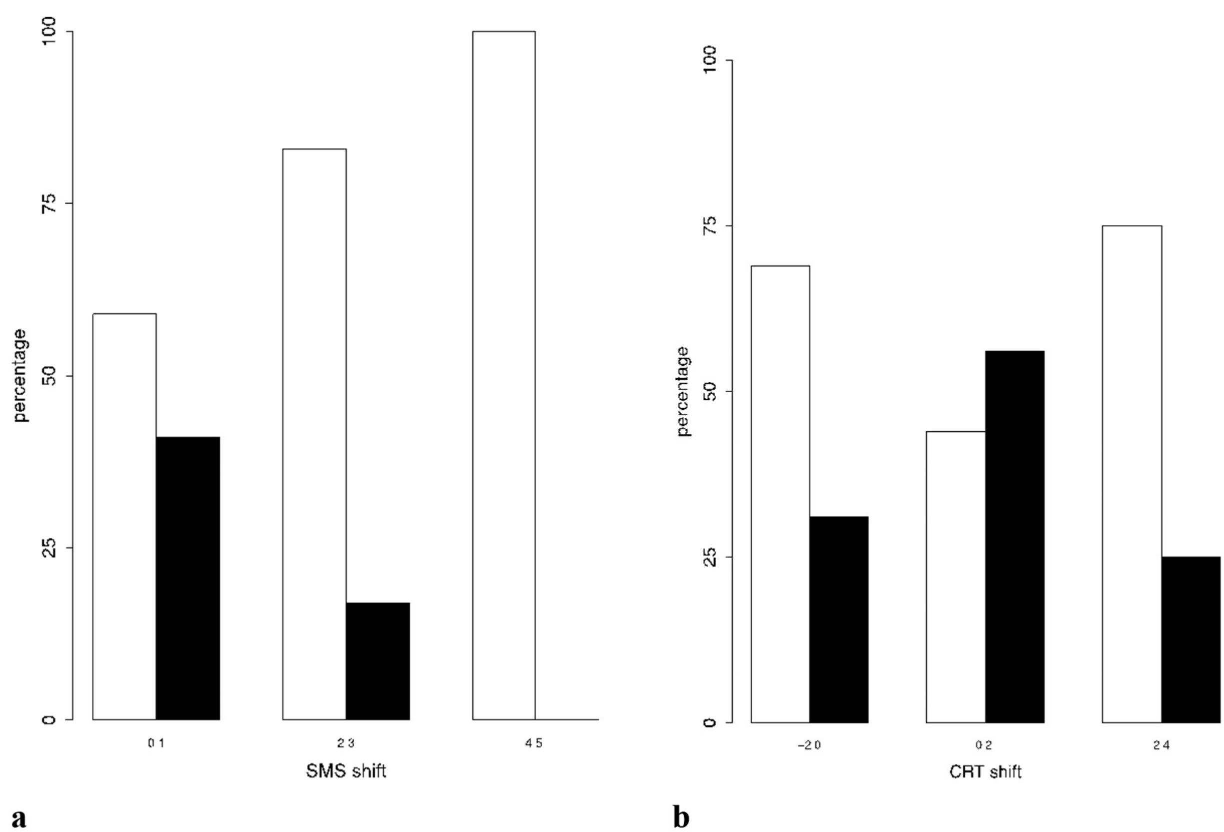


**Fig. 2.** Deceased and alive patients at day 28 in the predefined categories of skin mottling score shift (2a) and capillary refill time shift (2b). Results are given as percentage. White plots represent alive patients, and black plots represent deceased patients.

**Table 3**
Univariate analysis of factors associated with mortality at day 28 of patients with septic shock cared for in the prehospital setting prior to ICU admission.
Initial variables were collected in the prehospital setting at first medical contact and finial variables at ICU admission. Data are presented as *p* value and Odds Ratio (OR) with a 95% confidence interval [CI95]

| | OR [CI95] | *p value* |
|---|---|---|
| Age (years) | 1.01 [0.98–1.05] | 0.46 |
| Weight (kg) | 0.95 [0.95–1.03] | 0.68 |
| Size (cm) | 0.98 [0.91–1.04] | 0.48 |
| Initial SBP (mm Hg) | 1.00 [0.98–1.01] | 0.79 |
| Initial DBP (mm Hg) | 1.00 [0.98–1.02] | 0.99 |
| Initial MBP (mm Hg) | 1.00 [0.98–1.02] | 0.96 |
| Initial HR (bpm) | 0.99 [0.97–1.01] | 0.12 |
| Initial RR (mpm) | 1.03 [0.97–1.10] | 0.29 |
| Initial pulse oximetry (%) | 0.98 [0.94–1.01] | 0.19 |
| Initial temperature (°C) | 1.09 [0.88–1.40] | 0.46 |
| Initial blood glucose (mmol/l) | 0.95 [0.86–1.03] | 0.26 |
| Initial Glasgow coma scale | 0.97 [0.84–1.14] | 0.74 |
| Initial SMS | 1.49 [1.08–2.15] | 0.02* |
| Initial CRT (sec) | 1.53 [1.04–2.37] | 0.04* |
| Fluid volume expansion (ml) | 1.00 [0.99–1.01] | 0.09 |
| Norepinephrine dose ($mg \cdot h^{-1}$) | 0.66 [0.21–1.83] | 0.44 |
| Final SBP (mm Hg) | 0.97 [0.94–0.99] | 0.01* |
| Final DBP (mm Hg) | 0.96 [0.93–0.99] | 0.02* |
| Final MBP (mm Hg) | 0.96 [0.92–0.99] | 0.02* |
| Final HR (bpm) | 0.99 [0.98–1.01] | 0.49 |
| Final RR (mpm) | 1.04 [0.98–1.10] | 0.19 |
| Final pulse oximetry (%) | 0.98 [0.92–1.02] | 0.36 |
| Final temperature (°C) | 1.02 [0.83–1.27] | 0.87 |
| Final blood glucose (mmol/l) | 0.98 [0.89–1.07] | 0.65 |
| Final Glasgow coma scale | 0.90 [0.74–1.09] | 0.28 |
| Final SMS | 1.59 [1.12–2.37] | 0.01* |
| Final CRT (sec) | 1.29 [0.92–1.91] | 0.16 |
| SMS shift ($h^{-1}$) | 0.97 [0.63–1.49] | 0.89 |
| CRT shift ($sec \cdot h^{-1}$) | 1.19 [0.78–1.91] | 0.44 |
| Prehospital duration (min) | 1.01 [0.99–1.02] | 0.35 |
| ICU length of stay (days) | 0.93 [0.85–1.01] | 0.13 |
| IGS2 | 1.06 [1.03–1.11] | 0.002* |
| SOFA score | 1.45 [1.21–1.83] | <0.001* |
| Gender | 1.55 [0.53–4.50] | 0.42 |
| HBP history | 1.36 [0.50–3.75] | 0.54 |
| Coronaropathy | 1.52 [0.34–6.38] | 0.56 |
| Cardiac insufficiency | 2.93 [0.45–23.56] | 0.26 |
| Chronic kidney disease | 1.09 [0.21–4.88] | 0.92 |
| Diabetes | 0.69 [0.21–2.06] | 0.52 |
| COPD | 0.89 [0.12–4.93] | 0.89 |
| Cancer | 0.68 [0.19–2.15] | 0.52 |
| Immunodepression | 1.20 [0.38–3.63] | 0.75 |
| HIV | 3.82 [0.35–84.88] | 0.29 |

Legend: SBP = systolic blood pressure (mmHg), DBP = diastolic blood pressure (mmHg), MBP = mean blood pressure (mmHg), RR = respiratory rate (movement per minute), HR = heart rate (beats per minute), SMS = skin mottling score, CRT = capillary refill time (sec), ICU = intensive care unit, IGS=Index Gravity Score, SOFA = Sequential Organ Failure Assessment, HBP = high blood pressure, COPD = Chronic Obstructive Pulmonary Disease and HIV = human immunodeficiency virus.

norepinephrine infusion with a mean dose of 1.1 ± 0.8 $mg.h^{-1}$ in the prehospital setting with no significant differences between alive and deceased patients ($p = 0.44$).

Thirteen (21%) patients received antibiotic in the prehospital setting, mainly cefotaxime (77%). There was no missing data for initial and final SMS and CRT values.

SMS measured at the first medical contact in the prehospital setting was 3 ± 2 and was significantly different between alive and deceased patients (3 ± 2 vs 4 ± 1 respectively, $p = 0.02$) (Table 1). The mean SMS value at ICU admission was 3 ± 2 in the overall population and was significantly different between alive and deceased patients (3 ± 2 vs 4 ± 1 respectively, $p = 0.01$) (Table 1). SMS shift was measured at −0.05 ± 1.15 in the overall population, and at −0.05 ± 1.32 vs −0.05 ± 0.77 in alive and deceased patients respectively, with no difference ($p = 0.97$) (Table 1).

Prehospital mean CRT was of 5 ± 1 s. in the overall population, and 4 ± 1 s. vs 5 ± 1 s. in alive and deceased patients respectively. A significant difference was observed for CRT measured in the prehospital setting in alive and deceased patients ($p = 0.04$) (Table 1). Mean final CRT reached 5 ± 2 s. in the overall population, 5 ± 1 s. in alive patients and 5 ± 2 s. in deceased patients. No difference was found between alive and deceased patients for the mean final CRT measured at ICU admission ($p = 0.16$) (Table 1). CRT shift was measured at −0.3 ± 1.3 s. in the overall population. CRT shift was not different between alive and deceased patients and reached −0.04 ± 1.4 s. vs −0.01 ± 1.0 s respectively ($p = 0.97$) (Table 1).

Mortality increased with the increase in SMS scoring according to the predefined categories (Fig. 1a) and with increased CRT (Fig. 1b). No alive patients presented normal CRT (0–2.5).

We observed a correlation between mortality at day 28 and SMS shift (Fig. 2a). No correlation was found between mortality and CRT shift (Fig. 2b).

In the univariate analysis, mortality at day 28 was significantly associated with prehospital SMS ($p = 0.02$, OR [CI95] = 1.49 [1.08–2.15]), prehospital CRT ($p = 0.04$, OR [CI95] = 1.53 [1.04–2.37]), final SMS ($p = 0.01$, OR [CI95] = 1.59 [1.12–2.37]), final systolic blood pressure ($p = 0.01$, OR [CI95] = 0.97 [0.94–0.99]), final diastolic pressure ($p = 0.02$, OR [CI95] = 0.96 [0.93–0.99]) and final mean blood pressure ($p = 0.02$, OR [CI95] = 0.96 [0.92–0.99]) (Table 3).

After dichotomization of CRT and SMS using pre-specified thresholds, an association with mortality at day 28 was observed for SMS > 2 ($p = 0.04$, OR [CI95] = 3.01 [1.01–10.42] and for CRT > 4 s. ($p = 0.04$ OR [CI95] = 3.33 [1.12–10.95]).

After adjusting for confounding factors using propensity score, the relative risk of death at day 28 was 6.58 for SMS > 2 and 2.03 for CRT > 4 s. No covariates significantly differed between cases and controls (Table 4). Standardized mean deviation between the groups are presented in Fig. 3 (SMS > 2) and Fig. 4 (CRT > 4).

**Table 4**
Comparison of predictive variable for mortality at day 28 included in the propensity score before and after matching.
Values are expressed as mean ± SD or number (%). d corresponds to the standard mean deviation.

| PS covariate | Cases | Controls | p Value (d*) | Cases | Controls | p Value (d*) |
|---|---|---|---|---|---|---|
| SMS > 2 | Before matching $n = 67$ | | | After matching $n = 56$ | | |
| | n = 41 | $n = 17$ | | n = 41 | $n = 15$ | |
| Age | 73 ± 13 | 70 ± 16 | 0.15 | 72 ± 13 | 74 ± 14 | 0.12 |
| LOS ICU | 8 ± 7 | 9 ± 6 | 0.04 | 8 ± 7 | 9 ± 6 | 0.02 |
| IS | 11 (27%) | 5 (23%) | 0.12 | 11 (27%) | 3 (20%) | 0.09 |

Legend: PS: propensity score, LOS ICU: length of stay in intensive care unit, IS: immunosuppression

| CRT > 4 | Before matching n = 67 | | | After matching $n = 40$ | | |
|---|---|---|---|---|---|---|
| | $n = 23$ | $n = 44$ | | $n = 17$ | n = 23 | |
| SBP | 102 ± 42 | 93 ± 40 | 0.24 | 102 ± 42 | 101 ± 26 | 0.04 |
| Temperature | 37.3 ± 2.3 | 37.6 ± 2.4 | 0.09 | 37.4 ± 2.3 | 37.3 ± 2.4 | 0.04 |
| LOS ICU | 8 ± 6 | 9 ± 7 | 0.26 | 8 ± 6 | 8 ± 7 | 0.11 |
| Age | 74 ± 11 | 70 ± 15 | 0.28 | 74 ± 11 | 71 ± 15 | 0.18 |

Legend: PS: propensity score, SBP: systolic blood pressure, LOS ICU: length of stay in intensive care unit.

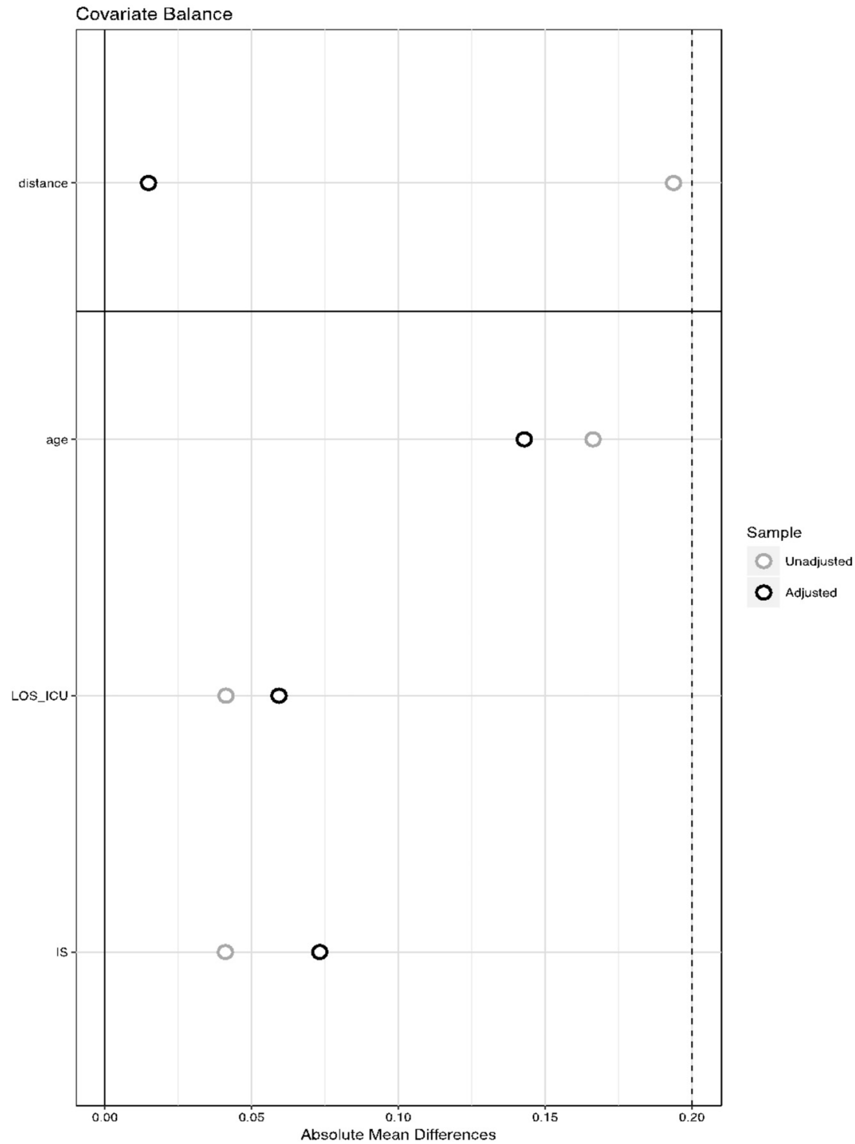


**Fig. 3.** Standard mean deviation between cases (SMS > 2) and controls (SMS < 2) after matching on propensity score.

## 4. Discussion

In the herein work including 63 patients with septic shock initially cared in the prehospital setting by a MICU team and admitted to the ICU, prehospital SMS and CRT were associated with mortality at day 28. A SMS > 2 or a CRT > 4 s were associated with a 6-fold and 2-fold increase in mortality at day 28 respectively. SMS and CRT are simple, non-invasive parameters to evaluate the microcirculation in the prehospital setting.

In septic shock, relative and absolute hypovolemia are compensated by vasoconstriction to maintain optimal blood pressure and organ perfusion. Septic shock preferentially affects the microcirculation [6, 17], leading to multiple organ failure and thus mortality [28]. Monitoring of the microcirculation status was shown to have a strong prognosis value in septic shock [29, 30]. Early bedside exploration of the microcirculation, using clinical and biological parameters, is therefore crucial [29, 30]. In-hospital monitoring of the microcirculation is preferentially performed using blood lactate and near-infrared spectroscopy (NIRS). As biological parameters are limited in the prehospital setting, emergency physicians focused on clinical hallmarks reflecting dysfunctions of the microcirculation. To this matter, CRT and SMS measurements gain of interest. If both clinical tools do not replace biological parameters such as blood lactate, but can be helpful in the prehospital setting. Indeed, a relationship between SMS, CRT and blood lactate level was previously reported [17, 31]. Interestingly, in hospital setting, blood lactate well correlated with SMS and CRT, whereas NIRS did not despite its promising results for risk stratification in septic shock [32].

In this work, we monitored the microcirculation in patients with septic shock cared for in the prehospital setting with SMS and CRT. The absolute value and the kinetic (shift) of these tools were measured in/between the first prehospital medical contact and ICU admission.

The absence of significant results concerning SMS and CRT shift can result from one of the following explanations. First, the lack of power of our work due to a small sample size may have missed out on a possible association. Second, the evaluation of reported values of SMS and CRT may lack precision as there are subjective markers retrieved from medical records despite the use of a watch timer and a chart. Finally, the relative short duration of the prehospital care of around 90 min, may be insufficient to observe the benefits of treatments on the microcirculation status, and thus a significant improvement in the scoring of both SMS and CRT.

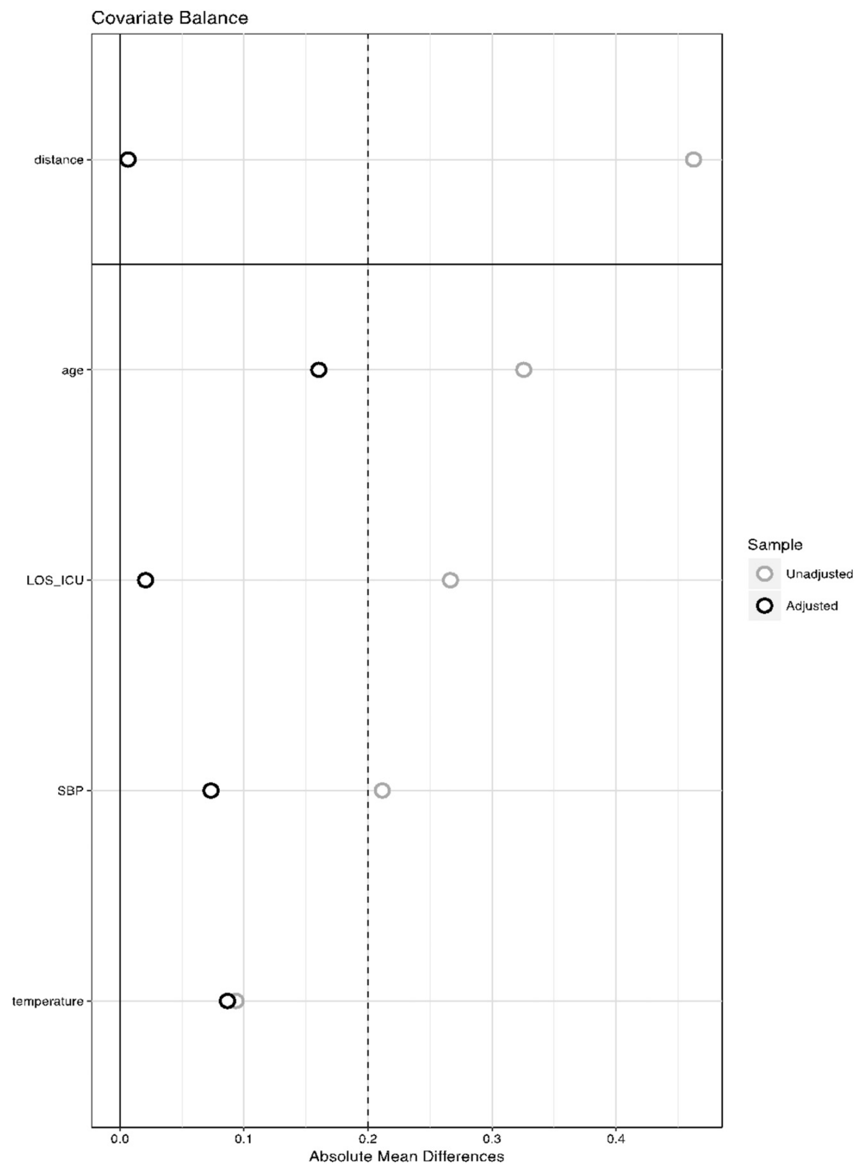


**Fig. 4.** Standard mean deviation between cases (CRT > 4) and controls (CRT < 4) after matching on propensity score.

## 5. Limitations

This works presents limitations. This study is retrospective and monocentric. Moreover, bias from misclassification of evaluated covariate (SMS and CRT) might exist, as data were collected from prehospital and ICU medical reports. In addition, the study was not designed to determine a threshold for prehospital values of SMS and CRT above which mortality is increased and neither to conclude in a causality link between mortality and the clinical tools. Next, intrinsic limitations of SMS and CRT should be kept in mind. Clinical practice and interpretation of SMS and CRT may widely vary within individuals and centres, due to the lack of recommendations [12]. For instance, no guidelines exist on the preferential site of measurement, the firmness and the compression time [12]. SMS is also more difficult to assess in patients with dark skins [33, 34]. Both SMS and CRT evaluation are subjective and can be affected by others factors (environmental, skin and core temperatures, age, ambient light conditions) [35]. Outside intrinsic limitations of these clinical parameters, pathological threshold for CRT in septic shock remains undetermined. It is difficult to assess the normal status of the patient's microcirculation during septic shock. Consequently, in pathological situations, the monitoring of a value and the evaluation of its dynamic evolvement, i.e. kinetic, may be more relevant than absolute values [16, 36]. At last, our work focused on patients with septic shock, in which, vascular phenomenon are different from other aetiologies of shock and may not be extrapolated to other clinical situations.

Still, despite the lack of power, we found a significant association between mortality at day 28 and prehospital SMS and CRT. Interestingly, blood pressure, a well-known prognosis factor in septic shock was associated with mortality in this analysis. Anyhow, larger cohorts are required to confirm these preliminary findings and to further explore the potential benefit to assess SMS and CRT shift in the early evaluation of treatment efficiency.

Consequently, we suggest using prehospital SMS and CRT as valuable tools in the evaluation of patient's outcome in the prehospital management of septic shock. SMS and CRT may be used as dynamic indicators to appraise the microcirculation.

## 6. Conclusion

Alteration of the microcirculation reflects the severity of septic shock and can be assessed using both SMS and CRT. In this work, we report an association between prehospital SMS and in-hospital mortality at day

28. We suggest using SMS as a hallmark of the microcirculation status in the prehospital setting to predict mortality of patients with septic shock. These parameters can help the physician optimize the management of patients with septic shock cared for in the prehospital setting. These results still warrant further studies.

## Conflicts of interest

The authors report no conflicts of interest.

## Authors contribution

- Study concept and design: Jouffroy.
- Acquisition of data: Jouffroy.
- Analysis and interpretation of data: Jouffroy.
- Drafting of the manuscript: Jouffroy, Saade.
- Critical revision of the manuscript for important intellectual content: Tourtier, Ecollan, Gueye, Bloch-Laine, Carli, Vivien.

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