Septic Shock: Phenotypes and Outcomes

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ABSTRACT

Introduction: Sepsis is a heterogeneous syndrome that results in life-threatening organ dysfunction. Our goal was to determine the relevant variables and patient phenotypes to use in predicting sepsis outcomes.

Methods: We performed an ancillary study concerning 119 patients with septic shock at intensive care unit (ICU) admittance (T0). We defined clinical worsening as having an increased sequential organ failure assessment (SOFA) score of ≥1, 48 h after admission (ΔSOFA ≥ 1). We performed univariate and multivariate analyses based on the 28-day mortality rate and ΔSOFA ≥ 1 and determined three patient phenotypes: safe, intermediate and unsafe. The persistence of the intermediate and unsafe phenotypes after T0 was defined as a poor outcome.

Results: At T0, the multivariate analysis showed two variables associated with 28-day mortality rate: norepinephrine dose and serum lactate concentration. Regarding ΔSOFA ≥ 1, we identified three variables at T0: norepinephrine dose, lactate concentration and venous-to-arterial carbon dioxide difference (P(v-a)CO₂). At T0, the three phenotypes (safe, intermediate and unsafe) were found in 28 (24%), 70 (59%) and 21 (18%) patients, respectively. We thus suggested using an algorithm featuring norepinephrine dose, lactate concentration and P(v-a)CO₂ to predict patient outcomes and obtained an area under the curve (AUC) of 74% (63–85%).

Conclusion: Our findings highlight the fact that identifying relevant variables and phenotypes may help physicians predict patient outcomes.

Keywords: Septic shock; Norepinephrine; Lactate; Venous-to-arterial carbon dioxide partial pressure difference (P(v-a)CO₂);
Sequential organ failure assessment (SOFA) score; Phenotype

**Key Summary Points**

**Why carry out this study?**

Septic shock is a syndrome that encompasses a heterogeneous group of patients with various responses to treatments and, therefore, different evolution probabilities.

The early identification of patient subgroups at risk of poor outcomes may facilitate clinical management and improve the information delivered to relatives.

However, the role of the available bedside variables to facilitate the identification of patients who are at risk of clinical worsening or death remains controversial.

**What was learned from the study?**

Our ancillary study explored various patient phenotypes in the early stages of septic shock because not all patients are equal in terms of outcomes.

Three phenotypes were identified in patients with septic shock during the first day (safe, intermediate and unsafe).

We identified a phenotype in which clinical courses and outcomes are uncertain (intermediate phenotype).

We showed that a combination of bedside-available information (norepinephrine dose, serum lactate concentration and \(P(v-a)\)CO\(_2\)) can help clinicians to improve the prediction of outcomes in a predefined subgroup of patients with septic shock and uncertain outcomes.

**INTRODUCTION**

Sepsis and septic shock result in life-threatening organ dysfunctions, which are caused by a dysregulated host response to infection [1, 2]. Sepsis thus poses a healthcare challenge, with an estimated 10.7 million cases occurring worldwide annually [3]. The incidence of septic shock also increases by up to 13% each year, and its mortality rate remains over 50% [4, 5].

At the bedside, several clinical and biological variables are available to facilitate the identification of patients who are at risk of clinical worsening or death and thus require prompt haemodynamic optimisation [6]. According to the Surviving Sepsis Campaign, the early recognition and management of sepsis is associated with better outcomes [7]. However, the role of the available bedside variables remains controversial [8, 9]. Many studies evaluating the use of early goal-directed therapy (EGDT), which aims to optimise blood pressure, preload status and tissue perfusion in patients with sepsis, have shown minimal results [10–12]. The normalisation of central venous oxygen saturation (ScvO\(_2\)) may not rule out persistent tissue hypoperfusion, and ScvO\(_2\) levels above 80% have been associated with increased mortality in patients undergoing septic shock [13–15].

Lactate and its clearance have also been suggested as a resuscitation endpoint in septic shock [7]. Nevertheless, given the abnormal metabolism in cases of sepsis [16] and the decreased clearance of lactate [17], even the restoration of microcirculatory perfusion in these conditions may still be associated with increased serum lactate concentrations [18]. Thus, especially in septic shock, the exclusive use of increased serum lactate concentrations to determine the presence of tissue hypoxemia after the initial period of resuscitation may be limited [19–22]. In a previous prospective, observational and multicentric trial, we observed that increased venous-to-arterial carbon dioxide partial pressure difference (\(P(v-a)\)CO\(_2\)) was associated with poor outcomes in the early phase of septic shock, independent of ScvO\(_2\) or serum lactate concentrations [22–24].
Moreover, septic shock is a syndrome that encompasses a heterogeneous group of patients with various responses to treatments and, therefore, different evolution probabilities. The early identification of patient subgroups at risk of poor outcomes may facilitate clinical management and improve the information delivered to relatives [25–27]. The concept of individualised medicine invites the identification of patient phenotypes with distinct clinical characteristics that respond to dedicated interventions [28].

We performed an ancillary study to assess whether phenotypes based on haemodynamic variables can help clinicians in the initial management of patients with sepsis. Our goal was to determine the usefulness of the various clinical and biological variables that are readily available in daily practice to predict short- and long-term sepsis outcomes.

METHODS

Setting

We carried out this ancillary study in three intensive care units (ICUs; ClinicalTrials.gov, identifier NCT03292120). The initial study was approved by the ethics committee of Nice University Hospital, France (Agreement number 2016-A00533-48). The ancillary study was also approved by the ethics committee of the French Society of Anaesthesia, Critical Care and Perioperative Medicine (SFAR), (Agreement number IRB 00010254-2022-078) and their opinion covers multiple hospitals. The requirement for written informed consent was waived because of this study’s strict observational design, according to French law [29]. However, we obtained the patient’s or relatives’ consent to use these data.

Patients

As reported previously in our first trial, we screened all patients with septic shock during their first 6 h after ICU admission from June 2016 to November 2018. To explain this choice, we believe that bedside-available tools are more discriminant at the early stage of septic shock. Thus, our T0 in this study corresponds to the first 6 h of septic shock. Septic shock was defined according to the international sepsis definitions available at the time of the study [30]. We excluded patients in whom septic shock was diagnosed after 6 h, those younger than 18 years old, pregnant women and patients with a do-not-resuscitate order. We did not exclude patients suffering from immunosuppression or genetic disorders. Moreover, patients who experienced premature death within 24 h were excluded from the analysis because the prognostic factors were consequently irrelevant. The three ICUs were organised as described by Leone et al. [31], and their clinical practices were in agreement with international and French national guidelines.

Measurements and Study Design

We prospectively collected the patient demographic variables from their electronic charts. Time 0 (T0) was set as soon as haemodynamic monitoring was set, i.e. 1 h after ICU admission.

The data were gathered upon ICU admission (T0), 6 h after admission (T6), 24 h after (T24) and 48 h after (T48). Haemodynamic variables were included as in our previous study [22]. The Simplified Acute Physiology Score (SAPS II) was collected upon admission [32]. The Sequential Organ Failure Assessment (SOFA) score was calculated at T0 and T48, as was the 28-day mortality rate [1, 33]. Clinical worsening was defined as an increase in global SOFA score of ≥ 1 within 48 h (ΔSOFA ≥ 1), as highlighted in our previous study showing that ΔSOFA ≥ 1 was associated with increased 28-day and ICU mortality rates [22].

Several variables were included in the univariate analysis to assess their associations with ΔSOFA ≥ 1 and the 28-day mortality rate: age, gender, body mass index, SAPS II, SOFA, mean arterial pressure (MAP), diuresis, fluid balance, norepinephrine dose, serum lactate concentration, P(v-a)CO₂, serum lactate concentration clearance from T0 to T6, ScvO₂, continuous cardiac index (CCI) and adjuvant inotrope
treatment. Then, the multivariate analysis was performed.

To identify distinct phenotypes in our cohort study, we went through several stages. First, we selected five discriminant variables that were available at the bedside to build these phenotypes at three time points (T0, T6 and T24) during the patients’ ICU stay. The variables included were primarily based on a literature review and those collected in our previous studies [22, 27, 34–37]. Norepinephrine dose, serum lactate concentration, MAP, P(v-a)CO₂ and CCI were selected (Table 3). Next, we used the hidden Markov model (HMM) to allocate each patient into one phenotype. This step will be described in detail in “Statistical Analysis”. We recognised three total phenotypes. The patients were classified into one of the phenotypes at three time points: T0, T6 and T24. Of note, each patient’s phenotype pattern could evolve over these three time points.

Table 3 shows the stark differences between the phenotypes regarding the 28-day mortality rate, clinical worsening (ΔSOFA ≥ 1) and SOFA score. The clinical course associated with these phenotypes seems inadequate given clinical practice. For example, phenotype 1 (safe) included those patients with the lowest norepinephrine doses and serum lactate concentrations at all time points, with a favourable clinical course (97% stable evolution during the first day). Conversely, phenotypes 2 and 3, intermediate and unsafe, included those patients with higher clinical worsening and 28-day mortality rates. Moreover, we identified a phenotype in which clinical courses and outcomes are uncertain (intermediate phenotype). Thus, after the analysis, we defined two potential outcomes, favourable and poor, with the latter being defined as the persistence of the intermediate or unsafe phenotypes after T0 (Fig. 2).

Outcome Measurement

The primary outcome was the variables associated with the 28-day mortality rate at T0 and T6. Potential associations between each variable and ΔSOFA ≥ 1 were assessed as secondary outcomes. Moreover, we examined the clinical course of our three phenotypes (safe, intermediate and unsafe) and two probability outcomes (favourable and poor).

To consider the ratio between a single variable and ten events (ΔSOFA ≥ 1 and/or 28-day mortality rate), we developed an algorithm including three relevant variables at T0 (identified in the multivariate analysis) to predict a favourable or poor outcome at T24.

Statistical Analysis

We expressed continuous variables as mean (standard deviation) or median values (interquartile range) as appropriate and compared the various septic shock phenotypes using analysis of variance (ANOVA), a Student’s t test for continuous variables and the Pearson chi-square test or Fisher’s exact test for discontinuous variables. The associations between the variables and potential risk factors were initially assessed using univariate analysis. The variables associated with the 28-day mortality rate and/or ΔSOFA ≥ 1 in the univariate analysis with a p value < 0.05 in at least one comparison were included in the multivariate analysis. Odds ratios (ORs) were displayed with a 95% confidence interval (CI). In order to assign patients to several phenotypes, we used the multi-profile HMM [38, 39]. The HMM allowed us to investigate the dynamics of the patients’ trajectories during their ICU stays. The HMM is a statistical model that can be used to describe the evolution of observed events that depend on internal factors that cannot be directly observed. It refers to the observed event as a symbol and the hidden factor underlying the observation as a state. The HMM also consists of two stochastic processes, namely an invisible process of hidden states and a visible process of observable symbols. The hidden states form a Markov chain, and the probability distribution of the observed symbol depends on the underlying state. For this reason, the HMM is also called a doubly embedded stochastic process [40]. Thus, the HMM aims to reveal hidden groups or patterns from observed data. It is similar to clustering techniques, but this method is more flexible.
Moreover, the HMM provides transition probabilities over time across different profiles to show the probability of transitioning from profile “I” to profile “J”.

Modelling observations in these two layers, one visible and the other invisible, is particularly useful because many real-world problems involve classifying raw observations into a number of categories or class labels that are more meaningful to us. The HMM has therefore been applied in a variety of fields, such as diabetes [41], breast cancer [42] and public health research [43].

For example, in our study, the observed data were the relevant variables of patients with septic shock recorded during their first 24 h after ICU admission. The hidden groups (states) were the patients’ latent phenotypes. The variables included in the HMM were described previously. Data may be missing from our HMM. The probability that a variable was missing is independent of the observed data and the other missing data. We observed less than 5% missing data (except for CCI). We used the Akaike and Bayesian information criteria (AIC and BIC) for model selection in HMM when the number of states is unknown. The model suggested two options: three or four phenotypes. After analysis, we also chose to build the HMM for three phenotypes because this was the most relevant to the patient outcomes analysis.

Finally, we developed an algorithm to predict outcomes through recursive partitioning analysis. This method resulted in a tree in which each branch shows the best distribution of patients according to a given variable threshold. All statistical analyses were performed using DMGM software and IBM SPSS version 20. A p value less than 0.05 was considered statistically significant.

RESULTS

During the study period, 207 patients were screened from our first trial, of whom 124 were eligible for this ancillary study. We excluded two (1.6%) patients after they denied permission to use their personal data for research purposes, as well as three (2.4%) others because of death within the first 24 h after ICU admission. As such, we analysed a total of 119 patients in this ancillary study (Fig. 1). Table 1 shows the patients’ characteristics. Upon ICU admission, the serum lactate concentration was 3.4 ± 2.6 mmol/l. The sources of septic shock were mainly the lungs (n = 44, 37%) and abdomen (n = 36, 30%). A ΔSOFA ≥ 1 occurred in 38 (32%) patients. The 28-day mortality rate was 30%.

At T0, the multivariate analysis showed two variables associated with the 28-day mortality rate: norepinephrine dose (OR 3.45 [95% CI 1.07–11.08]; p = 0.038) and serum lactate concentration (OR 1.32 [95% CI 1.08–1.61]; p = 0.006) (Table 2). Regarding ΔSOFA ≥ 1, we identified three variables at T0: norepinephrine dose (OR 5.25 [95% CI 1.47–18.74]; p = 0.011), serum lactate concentration (OR 1.51 [95% CI 1.18–1.92]; p < 0.001) and P(v-a)CO2 (OR 1.12 [95% CI 1.01–1.25]; p = 0.04). At T6, serum lactate concentration was associated with the 28-day mortality rate, but not with ΔSOFA ≥ 1 (Table 2). Moreover, the serum lactate clearance from T0 to T6 was associated with neither the 28-day mortality rate nor ΔSOFA ≥ 1.

At T0, the three phenotypes (safe, intermediate and unsafe) were distributed as follows: 28 (24%) patients in the safe phenotype, 70 (59%) in the intermediate phenotype and 21 (18%) in the unsafe phenotype (Table 3). In the safe phenotype, 26 (97%) patients were stable at T24. In the unsafe phenotype, 13 (62%) patients were stable at T24, while 8 (38%) proceeded to the intermediate phenotype. We thus assessed the statistical probability of remaining in the unsafe phenotype to be 77%.

From there, 40 (57%) patients in the intermediate phenotype did not evolve toward the safe phenotype, defined as a poor outcome, while 30 (43%) switched from the intermediate to the safe phenotype, defined as a favourable outcome (Fig. 2). We identified cut-off values for the three relevant variables at T0, which were included in our algorithm to predict a favourable or poor outcome (Fig. 3). We found the thresholds for norepinephrine dose, serum lactate concentration and P(v-a)CO2 to be 0.4 μg/kg/min, 3.5 mmol/l and 6 mmHg, respectively. With this algorithm, we obtained
an AUC of 74% (63–85%), with a sensitivity of 77%, a specificity of 68%, a positive predictive value of 64% and a negative predictive value of 79%.

DISCUSSION

The prediction of outcomes in cases of septic shock remains challenging. The exclusive use of each haemodynamic tool, independently of the others, to predict outcomes provides only incomplete information. Our goal in this project was to find the most powerful bedside-available variables to use in predicting outcomes. Moreover, our ancillary study explored various patient phenotypes in the early stages of septic shock because not all patients are equal in terms of outcomes. We focused on a group who are in the ‘grey zone’, excluding those with a major risk of early death and those with a high ratio of survival.

We found that norepinephrine dose is the best variable to use in predicting the 28-day mortality rate and/or a ΔSOFA ≥ 1 at T0 and T6. Serum lactate concentration seems more efficient in predicting the 28-day mortality rate than P(v-a)CO₂, which is more relevant in predicting ΔSOFA ≥ 1 at T0 and T6. At 24 h, we
identified three different phenotypes: safe, intermediate and unsafe. On the basis of the intermediate phenotype, we noted two patterns that can help clinicians predict favourable or poor outcomes. A combination of three variables—norepinephrine dose, serum lactate concentration and P(v—a)CO₂—provided the best level of outcome prediction, with an AUC of 74% (63–85%).

Our findings are in line with those reported in previous studies. Norepinephrine was found to be a strong determinant of patient outcomes. Several studies also explored the effects of MAP targets on patient outcomes [37, 44, 45]. A post hoc analysis of elderly patients in the SEP-SISPAM trial showed higher mortality rates among patients with higher MAP targets [44]. The guidelines for septic shock recommend, initially, at least 65 mmHg of MAP, followed by an individualised target [46]. However, Lamontagne et al. showed that lower blood pressure targets were not associated with adverse events in any subgroups, including patients with chronic hypertension [37]. Meanwhile, vasoressor use is not without risks [47]. Norepinephrine dose thus appears to be an independent factor associated with mortality [34].

### Table 1 Patients’ characteristics

| Variables                                      | Cohort (n = 119) |
|------------------------------------------------|------------------|
| Demographics                                   |                  |
| Age, mean ± SD, years                         | 65 ± 15          |
| Sex (male), n (%)                             | 79 (66)          |
| Body mass index, mean ± SD, kg/m²              | 25 ± 7           |
| SOFA score, median (Q25–Q75)                  | 9 (7–11)         |
| SAPS2 score, median (Q25–Q75)                 | 56 (46–68)       |
| Biological measurement, T0                    |                  |
| Lactate level, mmol/l, median (Q25–Q75)       | 3.4 (2.4–5.3)    |
| Arterial pH, median (Q25–Q75)                  | 7.3 (7.2–7.4)    |
| P(v—a)CO₂, mmHg, median (Q25–Q75)             | 6 (3–7.5)        |
| Evolution                                      |                  |
| 28-day mortality, n (%)                       | 36 (30)          |
| ΔSOFA ≥ 1                                     | 38 (31.9)        |
| Organ failure                                  |                  |
| Renal replacement therapy, n (%)              | 27 (22.7)        |
| Mechanical ventilation, n (%)                 | 92 (77.3)        |
| Norepinephrine dose at T0, µg/kg/min, median (Q25–Q75) | 0.45 (0.21–0.79) |
| Cumulative time of norepinephrine administration, h, median (Q25–Q75) | 49 (28–78)       |
| Terlipressin use, n (%)                       | 12 (10)          |
| Fluid balance at T72, mL, median (Q25–Q75)    | 892 (−350–(+)1982) |

Values are expressed as number (%), mean ± SD and median (Q25–Q75)

SOFA Sepsis-related Organ Failure Assessment, SAPS2 Simplified Acute Physiology Score II, ICU intensive care unit, ΔSOFA ≥ 1 SOFA score difference between T0 and T48
In an analysis derived from the Surviving Sepsis Campaign database, Casserly et al. showed that the hospital mortality of patients with septic shock increased in those with serum lactate concentrations above 4 mmol/L at T6 and arterial hypotension [48]. Similarly, Howell et al. found an increased risk of 28-day mortality for patients with serum lactate concentrations above 4 mmol/L [49]. However, in our study, lactate clearance was associated with neither a decrease in 28-day mortality rate nor ΔSOFA ≥ 1. Moreover, serum lactate concentration at T6 was not associated with ΔSOFA ≥ 1. Interestingly, we previously showed that lactate clearance was similar in patients with tissue hypoxia with or without achieving ΔSOFA ≥ 1 [22]. Finally, the usefulness of serum lactate concentration was higher in association with other tissue hypoxia variables [50].

In a prospective observational study, Ospina-Tascón et al. suggested that patients with persistently high P(v-a)CO2 at T6 had higher SOFA scores at day 3 than those with normalizing P(v-a)CO2 at T6 [24]. In 50 consecutive patients with septic shock, Vallée et al. found lower SOFA scores at T24 in patients with P(v-a)CO2 < 6 mmHg than in those with P(v-a)CO2 > 6 mmHg [51].

We evaluated three phenotypes based on the bedside-available variables. Identifying distinct clinical phenotypes may allow for more precise therapy and care improvement. For instance, Seymour et al. developed four clinical phenotypes correlated with clinical outcomes, and

| Variables          | Time | OR (95% CI)    | P value |
|--------------------|------|----------------|---------|
| Outcome: ΔSOFA ≥ 1 |      |                |         |
| Norepinephrine dose rate | T0   | 5.25 (1.47–18.74) | 0.011   |
|                     | T6   | 6.62 (1.90–23.10) | 0.003   |
| Lactate concentration | T0   | 1.51 (1.18–1.92)  | 0.001   |
|                     | T6   | 1.20 (0.95–1.50)  | 0.123   |
| MAP                | T0   | 0.98 (0.95–1.02)  | 0.331   |
|                     | T6   | 0.93 (0.89–0.98)  | 0.010   |
| P(v-a)CO2          | T0   | 1.12 (1.01–1.25)  | 0.040   |
|                     | T6   | 1.22 (1.02–1.46)  | 0.033   |
| Outcome: 28-day mortality |      |                |         |
| Norepinephrine dose rate | T0   | 3.45 (1.07–11.08) | 0.038   |
|                     | T6   | 3.14 (1.03–9.61)  | 0.045   |
| Lactate concentration | T0   | 1.32 (1.08–1.61)  | 0.006   |
|                     | T6   | 1.41 (1.10–1.81)  | 0.006   |
| MAP                | T0   | 0.98 (0.95–1.01)  | 0.217   |
|                     | T6   | 0.98 (0.94–1.03)  | 0.443   |
| P(v-a)CO2          | T0   | 0.95 (0.85–1.06)  | 0.390   |
|                     | T6   | 1.17 (0.99–1.39)  | 0.070   |

MAP mean arterial pressure, P(v-a)CO2 arterio-venous pressure difference in CO2, SOFA Sepsis-related Organ Failure Assessment, ΔSOFA ≥ 1 SOFA score difference between T0 and T48.
suggested that phenotype may help in understanding the heterogeneity of response to treatments in patients with sepsis [27]. In the same way, Gårdlund et al. identified six homogeneous subgroups within a complex phenomenon of patients with septic shock by estimating a categorical latent variable [52]. Decision-making based on conventional sepsis management can also lead to false judgments due to patient population heterogeneity [28].

Table 3 Phenotype groups characteristics and comparison

| Variables                          | Safe         | Intermediate | Unsafe        | P value |
|-----------------------------------|--------------|--------------|---------------|---------|
| Phenotype groups characteristics  |              |              |               |         |
| Lactate concentration, mmol/l, mean ± SD | T0 2.2 ± 0.7 | 3.9 ± 1.7   | 7.7 ± 3.3     |         |
|                                   | T6 2.0 ± 0.7 | 3.8 ± 1.6   | 8.5 ± 4.2     |         |
|                                   | T24 1.7 ± 0.6| 3.3 ± 1.5   | 10.4 ± 5.6    |         |
| Norepinephrine dose at T0, μg/kg/min, mean ± SD | T0 0.18 ± 0.09 | 0.56 ± 0.31 | 1.18 ± 0.88   |         |
|                                   | T6 0.22 ± 0.14 | 0.66 ± 0.29 | 1.76 ± 0.96   |         |
|                                   | T24 0.14 ± 0.12 | 0.59 ± 0.32 | 1.68 ± 1.19   |         |
| P(v-a)CO₂, mmHg, mean ± SD        | T0 5 ± 4     | 6 ± 4        | 8 ± 7         |         |
|                                   | T6 5 ± 3     | 6 ± 3        | 5 ± 3         |         |
|                                   | T24 5 ± 3    | 5 ± 3        | 9 ± 7         |         |
| MAP, mmHg, mean ± SD              | T0 75 ± 13   | 74 ± 13      | 64 ± 16       |         |
|                                   | T6 82 ± 10   | 72 ± 11      | 71 ± 10       |         |
|                                   | T24 82 ± 10  | 77 ± 9       | 78 ± 12       |         |
| CCI l/min/m², mean ± SD           | T0 3.7 ± 1.2 | 3.1 ± 1.0    | 3.3 ± 1.2     |         |
|                                   | T6 3.3 ± 0.9 | 3.0 ± 1.0    | 3.3 ± 1.4     |         |
|                                   | T24 3.7 ± 1.2| 3.3 ± 1.0    | 3.2 ± 1.2     |         |
| 28-day mortality, n (%)           | 2 (7.4)      | 20 (28.6)    | 14 (66.7)     | < 0.001 |
| ΔSOFA ≥ 1, n (%)                  | 2 (7.1)      | 21 (30)      | 15 (71.4)     | < 0.001 |
| SOFA, mean ± SD²                  | 8.18 ± 1.9β  | 9.01 ± 2.7δ  | 11.7 ± 3.1δ   | < 0.001 |
| SAPS2 score, mean ± SD²           | 49.4 ± 12.9β | 57.4 ± 14.8β | 67.4 ± 14.9δ  | 0.001   |
| Fluid balance at T24, ml, mean ± SD² | 2793 ± 2571β | 3197 ± 2546γ | 5874 ± 3969γ  | 0.010   |
| Pa/Fi ratio, mean ± SD²           | 272 ± 106β   | 226 ± 110β   | 173 ± 95δ     | 0.010   |

Values are expressed as number (%), mean ± SD
CCI: continuous cardiac index, P(v-a)CO₂: arterio-venous pressure difference in CO₂, MAP: mean arterial pressure, ΔSOFA: SOFA score difference between T0 and T48, SOFA: Sepsis-related Organ Failure Assessment, SAPS2: Simplified Acute Physiology Score II, Pa/Fi: oxygen arterial pressure over inhaled oxygen fraction ratio
²For P values: safe is compared to intermediate, intermediate to unsafe, and unsafe to safe
βP value > 0.05
γP value < 0.05
δP value < 0.01

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Individualised management in the early stages of septic shock appears to be the best response to the complex nature of these patients and the

Fig. 2 Evolution of the intermediate phenotype from T0 to T24. Intermediate intermediate phenotype patient subgroup, Safe safe phenotype patient subgroup, Unsafe unsafe phenotype patient subgroup.

Fig. 3 Algorithm including different variables at T0 to facilitate outcome predictions at T24. Poor poor outcome, Favourable favourable outcome.

Individualised management in the early stages of septic shock appears to be the best response to the complex nature of these patients and the
necessity of multiple, diverse and rapid management strategies [53].

During the first day, the safe and unsafe phenotypes had more predictable trajectories than the intermediate group. Altering the clinical trajectory of these patients is likely difficult. In contrast, more actions are possible in the intermediate phenotype. In our study, 40 (57%) patients with the intermediate phenotype had poor outcomes. We also showed a strong difference in the 28-day mortality rate and ΔSOFA ≥ 1 between favourable and poor outcomes. Thus, we found, among a large bundle of available haemodynamic variables, those associated with poor outcomes in a pre-defined group in which outcomes are uncertain (intermediate phenotype). This can help clinicians in identifying the duration of the optimisation phase duration in the haemodynamic management of septic shock [53].

The discriminant power of our algorithm is lower than expected, with an AUC of 74% (63–85%). We can explain this result on the basis of the persistence of a heterogenous group of patients. Indeed, Seymour et al. identified comorbidities and a state of inflammation as critical to defining sepsis phenotypes [27]. These variables were not reported in our study.

This ancillary study is not without limitations. First, pre-analytical errors may affect the findings based on biological variables. For the phenotype analysis, we focused on the intermediate phenotype because it was the only one that included patients evolving toward the safe phenotype. This allowed us to target those patients so as to identify the factors and values that affect outcomes. However, two patients in the safe phenotype group at T0 switched to the intermediate or unsafe phenotype at T24. These patients were not included in our analysis. One of these patients later endured ΔSOFA ≥ 1 and died within 28 days. Finally, our recursive partitioning analysis, which we used to build the algorithm, could be considered a simple association study, which suffers from the problem of multiple testing and a lack of external validation. Finally, a machine learning process has been used in other studies [54] to determine phenotypes, but our method provides another way to reach a similar goal.

Despite these limitations, the variables we studied are available at the bedside from admission to discharge, and they represent no additional cost. We showed that a combination of bedside-available information can help clinicians to improve the prediction of outcomes, in contrast to the relevance of a single variable. These variables can be used to define difficult-to-treat, or refractory, septic shock and introduce adjunctive therapy. This individualised patient care is in line with clinical practice guidelines for the management of sepsis and septic shock [7]. This can lead to improvements in the early management of septic shock and the information given to relatives about this life-threatening condition. When initial therapy, in the first 6 to 8 h of septic shock resuscitation, is aimed at decreasing our identified bedside-available variables in the predefined subgroup of patients with uncertain outcomes, this is likely to improve the outcomes of the patients.

CONCLUSION

Our findings underline the fact that a combination of norepinephrine dose, serum lactate concentration and P(v-a)CO₂ can be useful to predict patient outcomes in the early stages of septic shock. The novelty of this paper is the identification of a combination of discriminant haemodynamic variables in a predefined subgroup of patients with septic shock and uncertain outcomes. This combination of variables is available at the bedside, without delay or additional cost. Identifying patient phenotypes with uncertain clinical courses may further help physicians recognise patients with poor outcomes.

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Compliance with Ethics Guidelines. The initial study was approved by the ethics committee of Nice University Hospital, France (Agreement number 2016-A00533-48). The ancillary study was also approved by the ethics committee of the French Society of Anaesthesia, Critical Care and Perioperative Medicine (SFAR), (Agreement number IRB 00010254-2022-078) and their opinion covers multiple hospitals. The requirement for written informed consent was waived because of this study’s strict observational design, according to French law [29]. However, we obtained the patient’s or relatives’ consent to use these data.

Disclosures. All the authors have nothing to disclose.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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