Septic Shock: Phenotypes and Outcomes

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Abstract

Our goal was to determine the relevant variables and patient phenotypes to predict sepsis outcomes. We performed an ancillary study concerning 119 patients from three intensive care units (ICUs) in septic shock at ICU admittance (T0). We defined clinical worsening as having an increased Sequential Organ Failure Assessment (SOFA) score ≥ 1 48 hours after admission ($\Delta\text{SOFA} \geq 1$). We performed univariate and multivariate analyses according to 28-day mortality rate and $\Delta\text{SOFA} \geq 1$, and determined three patient phenotypes: safe, intermediate and poor. Persistence of the intermediate and poor phenotypes after T0 were defined as poor outcomes. At T0, the multivariate analysis showed two variables associated with 28-day mortality rate: norepinephrine dose and serum lactate concentration. Regarding $\Delta\text{SOFA} \geq 1$, we identified three variables at T0: norepinephrine dose, serum lactate concentration and venous-to-arterial carbon dioxide partial pressure difference (P(v-a)CO_2). At T0, the three phenotypes (safe, intermediate, and poor) were distributed in 28 (24%), 70 (59%) and 21 (18%) patients, respectively. We thus suggested an algorithm featuring norepinephrine dose, serum lactate concentration and P(v-a)CO_2 to predict patient outcomes and obtained an area under the curve (AUC) of 74% (63–85%). In conclusion, our findings underline that identifying relevant variables and phenotypes may help physicians recognize patient outcomes.

Introduction

Sepsis and septic shock result in life-threatening organ dysfunctions, 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. Septic shock incidence also increases by up to 13% each year and its mortality remains over 50% ^{4,5}.

At the bedside, several clinical and biological variables are available to facilitate the identification of patients at risk of clinical worsening or death, and thus requiring prompt hemodynamic optimization 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 bedside available variables remains controversial ^{8,9}.

The use of monitoring tools is controversial as well. For example, the normalization 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 ^{10–12}. Other hemodynamic tools have been less investigated with regard to their ability to predict patient outcomes in the early stages of septic shock.

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 the information delivered to

relatives^{13–15}. The concept of individualized medicine invites the identification of patient sub-phenotypes with distinct clinical characteristics that respond to dedicated interventions¹⁶.

In a previous prospective, observational and multicentric trial, we aimed to assess venous-to-arterial carbon dioxide partial pressure difference ($P(v-a)CO_2$) as a predictor of clinical worsening in patients with septic shock. Here, we performed an ancillary study to assess if phenotypes based on hemodynamic variables may help clinicians guide the initial management of patients with sepsis. Our goal was to determine the usefulness of the different clinical and biological variables 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 the Nice University Hospital, France (agreement number 2016-A00533–48). The requirement for written informed consent was waived due to this study's strict observational design according to French law¹⁷. However, we obtained the patient or relatives consent for using these data.

Patients

As reported previously in our first trial, we screened all patients with septic shock during their first 6 hours after ICU admission from June 2016 to November 2018. Septic shock was defined according to the international sepsis definitions available at the time of the study¹⁸. We excluded patients in whom septic shock was diagnosed after 6 hours, those younger than 18 years old, pregnant women and patients with a do-not-resuscitate order. Moreover, patients who experienced premature death within 24 hours were excluded from the analysis, as the prognostic factors were consequently irrelevant. The three ICUs were organized as described by Leone and al.¹⁹, and their clinical practices were in agreement with international and French national guidelines.

Measurements and study design

We prospectively collected the patients' demographic variables from their electronic charts. Time 0 (T0) was set as soon as hemodynamic monitoring was set, that is, 1 hour after ICU admission.

The data were gathered upon ICU admission (T0), 6 hours after admission (T6), 12 hours after (T12), 24 hours after (T24), 48 hours after (T48) and 72 hours after (T72). Hemodynamic variables were included as in our previous study²⁰. The Simplified Acute Physiology Score (SAPS II) was collected upon admission²¹. Sequential Organ Failure Assessment (SOFA) score was calculated at T0 and T48, as was 28-day mortality rate^{1,22}. Clinical worsening was defined as an increase in SOFA score ≥ 1 within 48 hours ($\Delta SOFA \geq 1$).

Several variables were included in the univariate analysis to assess their association with $\Delta\text{SOFA} \geq 1$ and 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)CO_2 , serum lactate concentration clearance from T0 to T6, ScvO_2 , continuous cardiac index (CCI) and adjuvant inotrope treatment. Then, the multivariate analysis was built.

Then, we determined different phenotypes using five variables measured during the patients' ICU stay: norepinephrine dose, serum lactate concentration, MAP, P(va)CO_2 , CCI (Table 3). We recognized three total phenotypes: safe, intermediate and poor. The safe phenotype encompassed patients with favourable outcomes, as opposed to the intermediate and poor phenotypes (Table 3). The patients were classified into one of the phenotypes at three timepoints: T0, T6 and T24. Of note, each patient's phenotype pattern could evolve during these three timepoints.

To this purpose, we used the multi-profile hidden Markov model (HMM) ^{23,24}. The HMM allowed us to investigate the dynamics of the patients' trajectories during their ICU stay. The HMM is a statistical model that can be used to describe the evolution of observed events which 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 ²⁵. Thus, the HMM aims to recover 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 overtime 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, since 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 ²⁶, breast cancer ²⁷ and public health ²⁸.

For example, in our study, the observed data were the relevant variables of septic shock patients recorded during their first 24 hours after ICU admission. The hidden groups (states) were the patients' latent phenotypes. The variables included in the HMM were primarily based on domain knowledge and a literature review, in addition with those collected for our study as defined previously ^{15,20,29,30}. We chose to build the HMM for 3 phenotypes for it was the most relevant for the patient outcomes analysis.

Finally, we used two outcomes: favourable and poor, with the latter defined as the persistence of the intermediate or poor phenotypes after T0.

Outcome measurement

The primary outcome was to assess the variables associated with 28-day mortality rate at T0 and T6. The associations between the variables and $\Delta\text{SOFA} \geq 1$ were then studied to assess the secondary outcomes. Moreover, we examined the clinical course of our three phenotypes (safe, intermediate and poor) and two probability outcomes (favourable and poor).

Additionally, we identified cut-off values for the clinical and biological variables at T0 to predict a favourable or poor outcome. Then, we developed an algorithm including these variables to facilitate clinical management in the early stages of septic shock.

Statistical analysis

We expressed continuous variables as mean (standard deviation) or median values (interquartile range) as appropriate, and compared between the different septic shock phenotypes using analysis of variance (ANOVA), 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 28-day mortality rate and/or $\Delta\text{SOFA} \geq 1$ in the univariate analysis, with a p -value < 0.05 in at least one comparison, were included in the multivariate analysis. Odds ratios (OR) were displayed with a 95% Confidence interval (CI). All statistical analyses were performed using DMGM software and IBM SPSS v20. A p -value less than 0.05 was considered statistically significant.

Results

During the study period, 207 patients were screened for our first trial, of whom 124 were eligible for this ancillary study. We excluded 2 (1.6%) patients after they denied permission to use their personal data for research purposes, as well as 3 (2.4%) for death within the first 24 hours 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 patient median serum lactate concentration was 3.4 ± 2.6 mmol/l. Septic shock occurred mainly due to pneumonia ($n = 44$, 37%) or intra-abdominal infections ($n = 36$, 30%). The 28-day mortality rate was 30%. A $\Delta\text{SOFA} \geq 1$ occurred in 38 (32%) patients.

To begin, we performed the univariate and multivariate analyses. At T0, the multivariate analysis showed two variables associated with 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, 1.09–1.61]; $p = 0.006$; Table 2). Regarding $\Delta\text{SOFA} \geq 1$, 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, 1.19–1.92]; $p < 0.001$) and P(v-a)CO_2 (OR, 1.12 [95% CI, 1.01–1.25]; $p = 0.04$). At T6, serum lactate concentration was associated with 28-day mortality rate. In contrast, serum lactate concentration was not associated with $\Delta\text{SOFA} \geq 1$ (Table 2). Moreover, the lactate clearance from T0 to T6 was associated with neither 28-day mortality rate nor $\Delta\text{SOFA} \geq 1$.

At T0, the three phenotypes (safe, intermediate and poor) were distributed as follows: 28 (24%) patients in the safe phenotype, 70 (59%) in the intermediate phenotype and 21 (18%) in the poor phenotype

(Table 3). In the safe phenotype, 26 of the 28 patients (97%) were stable at T24. In the poor phenotype, 13 of the 21 patients (62%) were stable at T24, while 8 (38%) proceeded to the intermediate phenotype. We thus assessed the statistical probability of remaining in the poor phenotype as 77%.

From there, 40 patients in the intermediate phenotype (57%) did not evolve towards the safe phenotype (defined as a poor outcome), while 30 (43%) switched from the intermediate to safe phenotype (defined as a favourable outcome; Fig. 2). Based on these two patterns, we derived an algorithm of different variables to facilitate outcome predictions in the early stages of septic shock (Fig. 3). With this algorithm, we obtained an area under the curve (AUC) of 74% (63–85%; sensitivity: 77%; specificity: 68%; positive predictive value: 64%; negative predictive value: 79%). We highlighted the thresholds for norepinephrine dose, serum lactate concentration and P(v-a)CO₂ as 0.4 µg/kg/min, 3.5 mmol/l and 6 mmHg, respectively.

Discussion

Our ancillary study explored the bedside available variables and different patient phenotypes in the early stages of septic shock to help clinicians predict patient outcomes. We found that norepinephrine dose is the best variable to predict 28-day mortality rate and/or $\Delta\text{SOFA} \geq 1$ at T0 and T6. Additionally, serum lactate concentration seems more suitable for predicting 28-day mortality rate, in contrast to P(v-a)CO₂, which is more relevant for predicting $\Delta\text{SOFA} \geq 1$. We also highlighted three phenotypes in patients with septic shock by T24: safe, intermediate and poor. Based on the intermediate phenotype patients, we noted two patterns to help clinicians predict favourable or poor outcomes. A combination of variables (norepinephrine dose, serum lactate concentration, and P(v-a)CO₂) provided the best level of outcome prediction.

Our findings are in line with those reported in previous studies. Norepinephrine was discovered to be a strong determinant of patient outcomes. Several studies also explored the effects of MAP targets on patient outcomes^{31–33}. A post-hoc analysis of elderly patients in the SEPSISPAM trial showed higher mortality in patients with higher MAP targets³¹. Guidelines for septic shock recommend initially at least 65 mmHg of MAP, followed by an individualized target³⁴. However, Lamontagne et al. showed that lower blood pressure targets were not associated with patient-important adverse events in any subgroup, including chronically hypertensive patients³². Meanwhile, vasopressor use is not without risks³⁵. Norepinephrine dose thus appears to be an independent factor associated with mortality²⁹.

In an analysis from the Surviving Sepsis Campaign database, Casserly et al. showed that the hospital mortality of patients with septic shock increased in patients with a serum lactate level above 4 mmol/L at T6 and arterial hypotension³⁶. Similarly, Howell et al. attested to an increased risk of 28-day in-hospital mortality for patients with a serum lactate level above 4 mmol/L³⁷. However, in our study, lactate clearance was associated with neither a decrease in 28-day mortality rate nor $\Delta\text{SOFA} \geq 1$. Moreover, serum lactate concentration at T6 was not associated with $\Delta\text{SOFA} \geq 1$. Interestingly, we previously

showed that lactate clearance was similar in patients with tissue hypoxia with or without achieving $\Delta\text{SOFA} \geq 1$ ²⁰. Finally, the usefulness of the serum lactate level was more suitable in association with another tissue hypoxia factor³⁸.

In a prospective observational study, Ospina-Tascon et al. indicated that patients with persistently high P(v-a)CO_2 at T6 had higher SOFA scores at day 3, as compared to those with a normalizing P(v-a)CO_2 at T6³⁹. In 50 consecutive patients with septic shock, Vallée et al. found lower SOFA scores at T24 in patients with low P(v-a)CO_2 values than in those with high P(v-a)CO_2 values, defining a threshold of P(v-a)CO_2 at 6⁴⁰.

We also evaluated a clinical model of the three phenotypes based on the available bedside variables. Identifying distinct clinical phenotypes may allow more precise therapy and care improvement. For instance, Seymour et al. developed four clinical phenotypes correlating with clinical outcomes, and suggested that phenotype may help in understanding treatment effect heterogeneity in patients with sepsis¹⁵. In the same way, Gardlund et al. identified six homogeneous subgroups within a complex phenomenon of patients with septic shock by estimating a categorical latent variable⁴¹. Decision making based on conventional sepsis management could also lead to false judgment due to patient population heterogeneity¹⁶. Individualized 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 strategies⁴². In our study, 40 patients had a poor outcome in the intermediate phenotype group. We also demonstrated a strong difference in 28-day mortality rate and $\Delta\text{SOFA} \geq 1$ between favourable and poor outcomes.

This ancillary study is not without several limitations. To begin, the biological parameter data have many pre-analytical error sources. Of note, 3 patients were excluded from the analysis due to death within T24, as these cases were considered too severe to include in the analysis of prognostic factors. For the phenotype analysis, we also chose to focus on the intermediate phenotype, as it was the only one that included patients evolving towards the safe phenotype. This allowed us to target those patients to identify the factors and values that affect outcomes. However, 2 patients in the safe phenotype group at T0 switched at T24 to the intermediate or poor phenotype. These patients were thus not included in our analysis. One of these patients later endured $\Delta\text{SOFA} \geq 1$ and deceased within 28 days. Despite these limitations, the variables we studied are available at the bedside from admission to discharge, and they have no additional cost. We showed that a combination of information might help clinicians better predict patient outcomes. This can lead to improvements in the early management of sepsis shock, or the information given to relatives about this life-threatening disease.

Conclusion

In conclusion, our findings underline that norepinephrine dose, serum lactate concentration and P(v-a)CO_2 can be useful tools to predict patient outcomes in the early stages of septic shock. Identifying different

clinical phenotypes may further help physicians recognize patients with poor outcomes.

Acronyms

- **ICU** : intensive care unit
- **T0**: admission time in ICU
- **T6** : 6-hour time from ICU admission
- **T24** : 24-hour time from ICU admission
- **SOFA** : Sequential Organ Failure Assessment
- **Δ SOFA ≥ 1** : increased SOFA score ≥ 1 48 hours after admission
- **OR** : odds ratio
- **CI** : confidence intervals
- **P(v-a)CO₂**: venous-to-arterial carbon dioxide partial pressure difference
- **AUC** : area under the curve
- **ScVO₂**: central venous oxygen saturation
- **SAPSII** : Simplified Acute Physiology Score II
- **MAP** : mean arterial pressure
- **CCI** : continuous cardiac index
- **HMM** : hidden Markov model

Declarations

Conflicts of interest and source of funding:

The authors report no conflict of interest in relation to the submitted study.

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Tables

Table 1.

Patients' Characteristics

Variables	Cohort (n=119)
Demographics	
Age, mean $\pm$ SD, y	65 $\pm$ 15
Sex (male), n (%)	79 (66)
Body mass index, mean $\pm$ SD, kg/m ²	25 $\pm$ 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)CO ₂ , mmHg, median (Q25-Q75)	6 (3-7.5)
Evolution	
28-day mortality, n (%)	36 (30)
Δ SOFA $\geq$ 1	38 (31,8)
Organ failure	
Renal replacement therapy, n (%)	27 (22.7)
Mechanical ventilation, n (%)	92 (77.3)
Norepinephrine dose at T0, μ g/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 $\pm$ SD and median (Q25-Q75). <i>SOFA</i> Sepsis-related Organ Failure Assessment, <i>SAPS2</i> Simplified Acute Physiology Score of 2, <i>ICU</i> Intensive Care Unit. Δ SOFA $\geq$ 1 = Clinical worsening: increase of the sequential organ failure assessment score (SOFA score) $\geq$ 1 (Δ SOFA $\geq$ 1) within two days	

Table 2.

Multivariate analysis for prognostic factors

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 level	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) CO ₂	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 level	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) CO ₂	T0	0,95 (0,85-1,06)	0,390
	T6	1,17 (0,99-1,39)	0,070
Δ SOFA ≥ 1 : SOFA score difference between T0 and T48. MAP: Mean Arterial Pressure, P(v-a)CO ₂ : arterio-venous pressure difference in CO ₂ , SOFA: Sepsis-related Organ Failure Assessment.			

Table 3.

Phenotype groups characteristics and comparison

Variables		Safe	Intermediate	Poor	P-value
Phenotype groups characteristics					
lactate level, mmol/l, mean $\pm$ SD	T0	2,2 $\pm$ 0,7	3,9 $\pm$ 1,7	7,7 $\pm$ 3,3	
	T6	2,0 $\pm$ 0,7	3,8 $\pm$ 1,6	8,5 $\pm$ 4,2	
	T24	1,7 $\pm$ 0,6	3,3 $\pm$ 1,5	10,4 $\pm$ 5,6	
Norepinephrine dose at T0, μ g/kg/min, mean $\pm$ SD	T0	0,18 $\pm$ 0,09	0,56 $\pm$ 0,31	1,18 $\pm$ 0,88	
	T6	0,22 $\pm$ 0,14	0,66 $\pm$ 0,29	1,76 $\pm$ 0,96	
	T24	0,14 $\pm$ 0,12	0,59 $\pm$ 0,32	1,68 $\pm$ 1,19	
P(v-a)CO ₂ , mmHg, mean $\pm$ SD	T0	5 $\pm$ 4	6 $\pm$ 4	8 $\pm$ 7	
	T6	5 $\pm$ 3	6 $\pm$ 3	5 $\pm$ 3	
	T24	5 $\pm$ 3	5 $\pm$ 3	9 $\pm$ 7	
MAP, mmHg, mean $\pm$ SD	T0	75 $\pm$ 13	74 $\pm$ 13	64 $\pm$ 16	
	T6	82 $\pm$ 10	72 $\pm$ 11	71 $\pm$ 10	
	T24	82 $\pm$ 10	77 $\pm$ 9	78 $\pm$ 12	
CCI, l/min.m ² , mean $\pm$ SD	T0	3,7 $\pm$ 1,2	3,1 $\pm$ 1,0	3,3 $\pm$ 1,2	
	T6	3,3 $\pm$ 0,9	3,0 $\pm$ 1,0	3,3 $\pm$ 1,4	
	T24	3,7 $\pm$ 1,2	3,3 $\pm$ 1,0	3,2 $\pm$ 1,2	
Phenotype groups comparison					
28-day mortality, n (%)		2 (7,4)	20 (28,6)	14 (66,7)	<0,001
Δ SOFA $\geq$ 1, n (%)		2 (7,1)	21 (30)	15 (71,4)	<0,001
SOFA, mean $\pm$ SD ^(a)		8,18 $\pm$ 1,9 ^(b)	9,01 $\pm$ 2,7 ^(d)	11,7 $\pm$ 3,1 ^(d)	<0,001
SAPS2 score, mean $\pm$ SD ^(a)		49,4 $\pm$ 12,9 ^(b)	57,4 $\pm$ 14,8 ^(b)	67,4 $\pm$ 14,9 ^(d)	0,001
Fluid Balance at T24, ml, mean $\pm$ SD ^(a)		2793 $\pm$ 2571 ^(b)	3197 $\pm$ 2546 ^(y)	5874 $\pm$ 3969 ^(y)	0,010
Pa/Fi ratio, mean $\pm$ SD ^(a)		272 $\pm$ 106	226 $\pm$ 110	173 $\pm$ 95	0,010

	(β)	(β)	(δ)
Values are expressed as number (%), mean $\pm$ SD.			
CCI: continuous cardiac index, P(v-a)CO ₂ : arterio-venous pressure difference in CO ₂ , MAP: Mean Arterial Pressure, Δ SOFA J0-J1: SOFA score difference between T24 and T48, SOFA: Sepsis-related Organ Failure Assessment, SAPS2: Simplified Acute Physiology Score 2, Pa/Fi: Oxygen arterial pressure over inhaled oxygen fraction ratio.			
α For P values: Safe is compared to Intermediate, Intermediate to Poor and Poor to safe.			
β P value > 0,05			
γ P value < 0,05			
δ P value < 0,01			

Figures

Figure 1

Consort diagram

Figure 2

Evolution of the intermediate phenotype from T0 to T24. Inter: intermediate phenotype patient subgroup; Safe: safe phenotype patient subgroup; Poor: poor phenotype patient subgroup.

Figure 3

Algorithm including different variables at T0 to facilitate outcome predictions at T24. Poor: poor outcome; Good: favourable outcome.