



Central venous oxygen saturation is not predictive of early complications in cancer patients presenting to the emergency department

Olivier Peyrony¹ · Guillaume Dumas² · Léa Legay¹ · Alessandra Principe¹ · Jessica Franchitti¹ · Marie Simonetta¹ · Anne Verrat¹ · Jihed Amami¹ · H  l  ne Milacic¹ · Ad  lia Bragan  a¹ · Ariane Gillet¹ · Matthieu Resche-Rigon^{3,4,5} · Jean-Paul Fontaine¹ · Elie Azoulay^{2,4,5}

Received: 26 June 2018 / Accepted: 6 October 2018 / Published online: 10 October 2018
  Societ  Italiana di Medicina Interna 2018

Abstract

Central venous oxygen saturation (ScvO₂) is easily observable in oncology patients with long-term central venous catheters (CVC), and has been studied as a prognostic factor in patients with sepsis. We sought to investigate the association between ScvO₂ and early complications in cancer patients presenting to the ED. We prospectively enrolled adult cancer patients with pre-existing CVC who presented to the ED. ScvO₂ was measured on their CVC. The outcome was admission to the intensive care unit (ICU) or mortality by day 7. ScvO₂ was first studied as a continuous variable (%) with a ROC analysis and as a categorical variable (cut-off at < 70%) with a multivariate analysis. A total of 210 cancer patients were enrolled. At baseline, ScvO₂ showed no significant difference between patients who were admitted to the ICU or died before day 7, and patients who did not (67%; IQR 62–68% vs. 71%; IQR 65–78% respectively, *P* = 0.3). The ROC analysis showed the absence of discrimination accuracy for ScvO₂ to predict the outcome (AUC = 0.56). By multivariate analysis, ScvO₂ < 70% was not associated with the outcome (OR 1.67; 95% CI 0.64–4.36). Variables that were associated with ICU admission or death by day 7 included a shock-index (heart rate/systolic blood pressure) > 1 and a performance status > 2 (OR 4.76; 95% CI 1.81–12.52 and OR 6.23, 95% CI 2.40–16.17, respectively). This study does not support the use of ScvO₂ to risk stratify cancer patients presenting to the ED.

Keywords Central venous oxygen saturation (ScvO₂) · Emergency department · Cancer · Triage · Neutropenia

Introduction

Identifying patients at high risk of early complications is a key goal of emergency departments (EDs). Initial triage is crucial to determine monitoring needs and administer initial treatment of patients visiting the ED to avoid serious complications [1]. The performance of several clinical (e.g., shock-index, mottling score) and biological markers (e.g., lactate levels) to optimize triage has been assessed [2–4]. Central venous oxygen saturation (ScvO₂) is a surrogate marker for mixed venous oxygen saturation (SvO₂) that reflects oxygen consumption over the entire body (imbalance between oxygen delivery and oxygen demand) and cardiac output [5, 6], and is measured by a catheter placed in the superior vena cava. To summarize, in case of increased oxygen demand to the tissues but without compensation by the cardiovascular system, the oxygen extraction by the tissues increases, resulting in a decrease of the ScvO₂. Thus,

✉ Olivier Peyrony
o.peyrony@hotmail.fr

¹ Emergency Department, H pital Saint-Louis, Assistance Publique-H pitaux de Paris (AP-HP), Paris, France

² Intensive Care Unit, H pital Saint-Louis, Assistance Publique-H pitaux de Paris (AP-HP), Paris, France

³ Biostatistics and Medical Information Department, H pital Saint-Louis, Assistance Publique-H pitaux de Paris (AP-HP), Paris, France

⁴ Centre of Research in Epidemiology and Statistics Sorbonne Paris Cit  (CRESS-INSERM-UMR1153), ECSTRRA Team, Paris, France

⁵ Paris Diderot University, Paris, France

a drop in ScvO₂ below 70% indicates a mismatch between O₂ need and O₂ delivery, and, in the absence of anemia, may also indicate a reduced cardiac output [7]. Therefore, ScvO₂ has been assessed to guide resuscitation in intensive care unit (ICU) patients suffering from early septic shock [8]. It has also been studied as a prognostic factor showing an increased mortality in case of low (<70%) ScvO₂ values in septic patients at ICU admission [9] or in the ED setting [10]. Immunocompromised patients, such as cancer patients, are at higher risk of septic complications than patients without malignancies [11]. Rapid recognition of cancer patients at risk of early complications would optimize standards of care for these patients, avoiding delays in initiating treatment and in ICU admission [12]. A biomarker allowing ED physicians to risk stratify patients at high risk of deterioration could improve the prognosis of this vulnerable population. ScvO₂ is easily observable in oncology and hematology patients with long-term central venous catheters (CVC) by drawing a blood gas sample on the CVC. The aim of this study was to investigate the association between ScvO₂ at ED admission, and subsequent need for ICU admission or early death in cancer patients already provided with a CVC presenting to the ED.

Methods

We prospectively enrolled patients with solid tumors or hematological malignancies visiting the ED of Hôpital Saint-Louis (Paris, France) between January and August 2015. The hospital has 650 beds, including 350 beds dedicated to curing malignancies. The ED receives 39,000 patients per year, including 15% of patients with malignancies. The medical ICU is a closed 12-bed unit that admits 600 patients per year, including about 130 cancer patients. ICU admission is considered when a cancer patient has at least one organ failure or with physiological derangements that foreshadows organ dysfunction. Early ICU admission is strongly encouraged to improve survival by preventing the development or progression of organ dysfunctions. Close collaboration between intensivists, onco-hematologists and emergency physicians is noteworthy to share discussions to decide which patients are the most likely to benefit from intensive care, and about the diagnostic workup and the goals of care.

Cancer patients receiving systemic chemotherapy, targeted therapies, stem cell transplantation, parenteral nutrition, or who are short of accessible peripheral veins, all carry a long-term CVC, usually in an internal jugular vein or sometimes in a subclavian vein. ScvO₂ measure is accessible by drawing a blood gas from the CVC. ED nurses are notably well trained to handle CVCs.

This was a convenience sample of patients who were included in the study if they (1) were adults (age > 18 years old), (2) carried a CVC, (3) required blood tests or intravenous access for monitoring or treatments, and (4) gave oral informed consent. After informed consent, a blood gas sample and a blood culture were taken from the CVC, in addition to routine biology tests required for patient management. Data abstracted from medical records included patient age, gender, malignancy location, performance status (PS), comorbidities, vital signs at triage including shock-index (heart rate/systolic blood pressure), mottling score (score 0 indicates no mottling; score 1, a modest mottling area (coin sized) localized to the center of the knee; score 2, a moderate mottling area that does not exceed the superior edge of the kneecap; score 3, a mild mottling area that does not exceed the middle thigh; score 4, a severe mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin) [3], biological data (such as lactate, creatinine, bicarbonate, white blood cell count and hemoglobin), results from blood cultures, ICU admission and vital status at day 7 and day 30. ScvO₂ data were not provided to managing clinicians. The outcome was defined as admission to the ICU or death within 7 days of ED management. Sepsis and septic shock were defined according to recent international definitions [13]. Neutropenia was defined as a leukocyte count < 1000 per mm³ or neutrophils < 500 per mm³. The study was approved by the regional Ethics Committee (Comité d'Evaluation de l'Ethique des projets de Recherche Biomedicale (CEERB) Paris Nord, number 15-002).

Statistical analysis

Results are reported as medians (with interquartile range), or as numbers (alongside percentages). Patient characteristics were compared using the Chi-square test or Fisher exact test, as appropriate, for categorical variables and the Wilcoxon test or Student *t* test, as appropriate, for continuous variables. We first plotted a receiver-operator-characteristic (ROC) curve and computed the area under the curve (AUC) to determine the discrimination of ScvO₂ at various thresholds. According to the admitted cut-off in the literature, we chose 70% to dichotomize the continuous variable into a binary variable. To investigate the association between ScvO₂ (< or ≥ 70%) and the outcome, we first performed a univariate analysis with each variable of interest. To investigate which variables were predictive of ICU admission or death by day 7 when considering confounders, multivariate logistic analysis was performed while including the variables with a *P* < 0.1 in the multivariate model. To preserve an event/variable ratio of 10%, clinically redundant variables were excluded. We then computed adjusted odds-ratios (OR) and their 95% confidence intervals (CI). Because ScvO₂ was

our variable of interest, we forced it into the final model. We also compared the ScvO₂ values between patient with or without positive blood culture. A sensitivity analysis was performed to explore the relationship between ScvO₂ and the outcome in the subgroup of patients suspected to have infection and in those with neutropenia. All tests were two-sided and *P* values were considered significant if they were less than 0.05. Analyses were performed using R software (version 3.4.2, The R Foundation, <http://www.r-project.org>).

Results

Patient characteristics

Over the study period, 210 patients were included. Patient characteristics are reported in Table 1. Half of the sample were men and the median age was 60 (49–69 years old). Two-thirds of patients had solid tumors and one-third had hematological malignancies. Forty-six (22%) patients had a poor performance status (severely altered or bedridden).

Patient characteristics in the ED are reported in Table 2. On arrival, 63 (30%) patients had a shock-index > 1 (meaning that their heart rate was over their systolic blood pressure) and only 6 (2%) patients had a mottling score ≥ 2. Among the 137 (65%) patients in which an infection was suspected, 33 (24%) had sepsis or septic shock. The most frequent suspected infection site was the lung (40%). Most patients with suspected infections received antimicrobial therapy. In 64% of cases, they were treated with a broad-spectrum beta lactam or a third-generation cephalosporin with activity against *Pseudomonas aeruginosa* or carbapenem, an aminoglycoside in 23% of cases and a glycopeptide in 10% of cases. Fifty-nine (28%) patients were neutropenic, of which 54 were febrile. Initial ScvO₂ was < 70% in 92 (44%) patients.

Association between ScvO₂ and the outcome

Outcome characteristics are reported in Table 3. The majority of patients were admitted to hospital. During their stay, 17 (8%) patients were admitted to the ICU. All ICU

Table 1 Patient characteristics on admission

	Patients, <i>N</i> (%) or median (IQR)—	Missing data
	<i>N</i> = 210	
Age (years)	60 (49–69)	
Men	104 (50)	
Underlying malignancy		
Solid malignancy	141 (67)	
Breast	54 (38)	
Digestive tract-pancreas	27 (19)	
Pulmonary-pleura	26 (18)	
Urology-kidney	14 (10)	
Hematological malignancy	69 (33)	
Lymphoma	26 (38)	
Leukemia	21 (30)	
Hodgkin	7 (10)	
Myeloma	7 (10)	
Allogeneic bone marrow transplant	9 (4)	
Performance status		
0	49 (23)	
1	65 (31)	
2	49 (23)	1
3	29 (14)	
4	17 (8)	
Comorbidities		
Diabetes mellitus	28 (13)	
Ischemic cardiomyopathy	13 (6)	
Chronic renal failure	12 (6)	
Chronic obstructive pulmonary disease	7 (3)	
HIV	6 (3)	

IQR interquartile range

Table 2 Patient characteristics on admission

	Patients, <i>N</i> (%) or median (IQR)— <i>N</i> =210	Missing data
Main reason of ED presentation		
Fever	108 (51)	
Asthenia	23 (11)	
Digestive	21 (10)	
Pulmonary	18 (9)	
Cytopenia	8 (4)	
Bleeding	6 (3)	
Neurological	5 (2)	
Pain	5 (2)	
Other	16 (8)	
Suspicion of infection		
Sepsis or septic shock	33 (24)	
Suspected infection location		
Pulmonary	29 (40)	
Skin-catheter	21 (19)	
Urinary tract	18 (17)	
Gastrointestinal	15 (14)	
Shock-index > 1	63 (30)	
Mottling score		
0	188 (90)	
1	16 (8)	
2	3 (1)	
3	0	
4	3 (1)	
5	0	
Transfusion		
Red cells	36 (17)	
Platelets	16 (8)	
Neutropenia	59 (28)	
Hemoglobin (g/dL)	10 (8.8–11.4)	
ScvO ₂ (%)	71 (64–78)	
ScvO ₂ < 70%	92 (44)	
Lactate > 2 (mmol/L)	43 (20)	7
Bicarbonate (mmol/L)		
≥ 20	166 (79)	
15–19	38 (18)	
< 15	6 (3)	

IQR interquartile range

admissions occurred in the first 7 days. Of the 17 critically ill patients, four died, including two before day 7. Ten (5%) patients died by day 7 and 27 (13%) patients by day 30. The outcome (death or ICU admission by day 7) occurred in 25 (12%) patients. Among these patients, 19 had severe sepsis or septic shock, 2 had hemorrhagic shock, 2 had malignancy progression, 1 had diabetes mellitus ketoacidosis and 1 had pulmonary edema and cardiac failure. There was no statistical difference in ScvO₂ values on admission

between patients who met the outcome and those who did not (ScvO₂ = 67% (62–68%) vs. 71% (65–78%), *P* = 0.3, Fig. 1). The ROC curve (Fig. 2) showed no discrimination accuracy for ScvO₂ to predict death or ICU admission by day 7 (AUC = 0.56).

Table 4 shows the results of univariate and multivariate analyses. Univariate analysis revealed that characteristics significantly associated with the need for ICU admission or death by day 7 included poor performance status (> 2), shock-index > 1, mottling score of 1 vs. 0, patients with sepsis or septic shock and bicarbonate level < 15 mmol/L. ScvO₂ values < 70% were not associated with the outcome in the univariate analysis. In the multivariate analysis, poor performance status (OR 6.23, 95% CI 2.40–16.17) and shock-index (OR 4.76, 95% CI 1.81–12.52) were independently associated with the need for ICU admission or death by day 7, whereas ScvO₂ values < 70% were not associated with the outcome.

ScvO₂ and positive blood cultures

Positive blood culture (excluding *Staphylococcus epidermidis*) occurred in 22 (10%) patients. ScvO₂ concentrations were not associated with the presence of blood stream infection (ScvO₂ = 71% (65–78%) vs. 70% (62–78%) in patients either with and without blood stream infection, respectively, *P* = 0.72).

Sensitivity analyses

Patients with suspected infection

Among patients with suspected infection (*N* = 137), 17 were admitted to the ICU or died by day 7. There was no difference in ScvO₂ concentrations between patients who were admitted to the ICU or died by day 7 and patients who did not (ScvO₂ = 67% (59–76%) vs. 71% (65–77%) respectively, *P* = 0.2, Fig. 3). Among the 17 patients who were admitted to the ICU or died by day 7, 10 (59%) presented ScvO₂ concentrations < 70% compared to 50 (42%) patients who were not admitted to the ICU and did not die (*P* = 0.28).

Patients with febrile neutropenia

Among patients with febrile neutropenia (*N* = 54), eight patients were admitted to the ICU or died by day 7. There was no significant differences of ScvO₂ concentrations between patients who were admitted to the ICU or died by day 7 and patients who did not (ScvO₂ = 61% (56–64%) vs. 72% (65–77%), *P* = 0.07, Fig. 3). Among the eight patients who were admitted to the ICU or died by day 7, seven (88%) presented ScvO₂ concentrations < 70%. In contrast,

Table 3 Bacteremia, intensive care unit admission and mortality

	Patients, <i>N</i> (%) or median (IQR)— <i>N</i> =210	Missing data
Positive blood cultures	45 (21%)	8
<i>Staphylococcus epidermidis</i>	23 (51)	
<i>Escherichia coli</i>	6 (13)	
<i>Pseudomonas aeruginosa</i>	5 (11)	
<i>Staphylococcus aureus</i>	4 (9)	
Central venous catheter ablation	19 (9)	
Admission		
Emergency short surveillance unit admission	112 (53)	
Ward admission	61 (29)	
ICU admission immediately from ED	8 (4)	
Discharge from hospital	29 (14)	
ICU admission throughout the hospital stay	17 (8)	
7-Day mortality	10 (5)	
30-Day mortality	27 (13)	
Death or ICU admission by day 7	25 (12)	
Death or ICU admission by day 30	40 (19)	

ED emergency department, ICU intensive care unit, IQR interquartile range

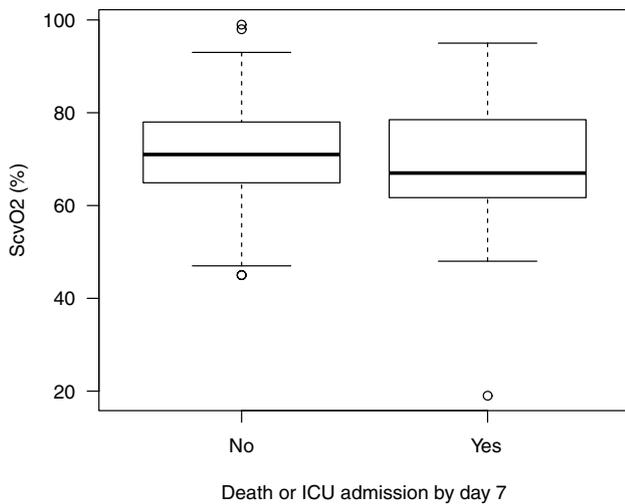


Fig. 1 Boxplot representing ScvO₂ values (median and 25th–75th centiles) according to the outcome (ICU admission or death by day 7)

19 (41%) patients who were not admitted to the ICU or died by day 7, presented ScvO₂ concentrations <70% (*P*=0.02).

Discussion

This study does not support the use of ScvO₂ for triage in cancer patients visiting the ED. Initial ScvO₂ values were not associated with the need for ICU admission or death by day 7 in overall patients, nor in the subgroup of patients with suspected infection. In contrast, patients with febrile

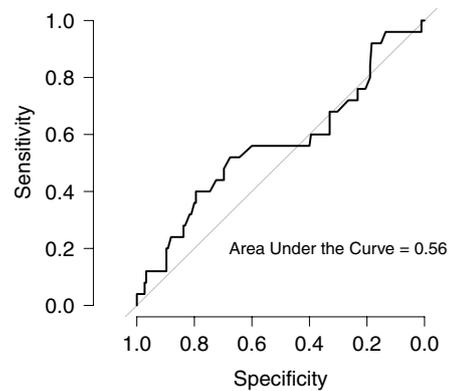


Fig. 2 Receiver operator characteristic curve plotting sensitivity and specificity of ScvO₂ for predicting the outcome (ICU admission or death by day 7)

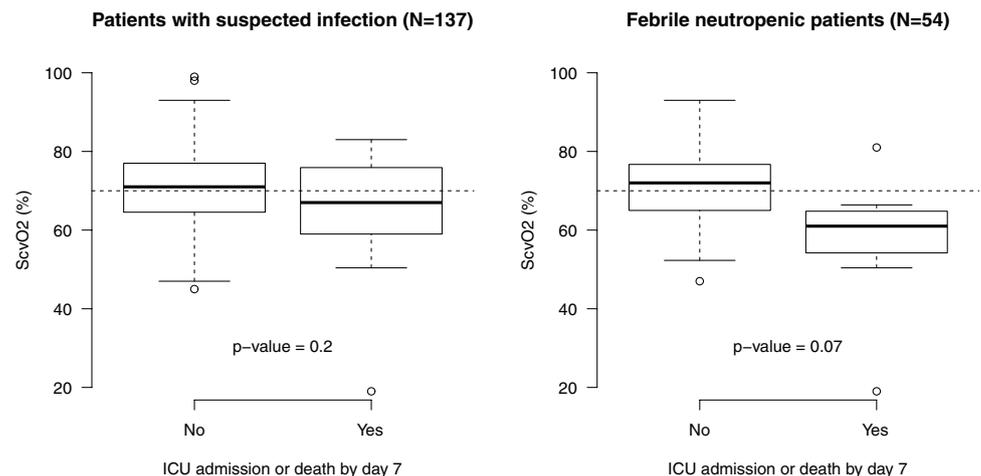
neutropenia who were admitted to the ICU or who died by day 7, more frequently had ScvO₂ values below 70% than patients who did not.

Triage and orientation is one of the cornerstones of emergency medicine. Thus, detection of early signs of physiological derangement is crucial to prevent the development of organ dysfunction by prompt treatment initiation and adequate monitoring. This evaluation is first based on clinical assessment and mostly on vital signs, which can be taken individually or jointly as the Quick Sequential Organ Failure Assessment (qSOFA) score (composed of respiratory rate ≥22 breaths/min, systolic blood pressure ≤100 mmHg, and altered mental status) or the shock-index, so as to increase accuracy in predicting mortality [14–17]. Close monitoring

Table 4 Univariate and multivariate logistic regression analysis to investigate the association between the covariates and primary outcome (intensive care unit admission or mortality by day 7)

	Univariate analyses			Multivariate analyses		
	Odds ratio	95% CI	<i>P</i> value	Adjusted odds ratio	95% CI	<i>P</i> value
Age (years)	1.01	0.98–1.04	0.45			
Performance status						
0–1–2	1			1		
3–4	8.28	3.33–20.6	<0.0001	6.23	2.40–16.17	<0.001
Shock index > 1	6.42	2.6–15.9	<0.0001	4.76	1.81–12.52	0.002
Mottling score						
0	1					
1	5.67	1.84–17.4	0.002			
≥2	1.89	0.21–17.1	0.58			
Suspicion of infection						
No sepsis	1					
Sepsis or septic shock	5.82	2.35–14.41	<0.001			
Neutropenia	1.5	0.6–3.6	0.35			
Hemoglobin (g/dL)	0.98	0.8–1.2	0.86			
Lactate (mmol/L)						
≤2	1					
>2	1.64	0.63–4.24	0.31			
Bicarbonates (mmol/L)						
≥20	1					
15–19	0.66	0.19–2.36	0.53			
<15	7.74	1.46–41.1	0.016			
ScvO ₂ < 70%	1.75	0.75–4	0.19	1.67	0.64–4.36	0.3

Fig. 3 Boxplot representing ScvO₂ values (median and 25th–75th centiles) according to the outcome (ICU admission or death by day 7) in patients with suspected infection (left) and in febrile neutropenic patients (right) subgroups. Dotted lines represent the ScvO₂ threshold of 70%



of patients vital signs and subtle clinical reassessment to detect beginning physiological derangements in the EDs may be defective due to overcrowding. Therefore, evaluation of additional biomarkers may be helpful in predicting clinical deterioration. For example, lactate has widely been studied in the emergency setting to predict mortality [18, 19], but the joining of lactate to clinical assessment is controversial [20]. Furthermore, cancer patients represent a frail population at high risk of acute complications among which sepsis

prevails [21, 22]. Even if cancer patients are of growing interest in emergency literature [23, 24], there is currently few tools to risk stratify these patients when they seek care in EDs. Recently, Boehm et al. showed that the deceleration capacity of the heart was a rapid non-invasive tool that predicted in-hospital mortality in 140 cancer patients presenting to the ED [25]. Other scores, such as the Multinational Association for Supportive Care in Cancer (MASCC) or the Clinical Index of Stable Febrile Neutropenia (CISNE) scores

have been studied in the emergency setting [26], but are specific of the febrile neutropenic patient. For these reasons, and owing to the fact that cancer patients often carry a CVC that allows easily measuring ScvO₂, we sought to investigate, in this pilot study, if this biomarker could predict early complications to avoid delays in managing these patients.

ScvO₂ is used to monitor the difference between oxygen delivery and oxygen consumption in tissues of septic patients. Under normal conditions, this difference is above 70%. Concentrations may fall under this value in shocked or dyspneic patients, or due to a shortfall in oxygen delivery (anemia, hypoxia, heart failure and hypovolemia) [6]. By targeting normal values of ScvO₂, as part of a bundle of measures for early goal directed therapy (EGDT) in ED septic patients with red blood cell transfusions or dobutamine, Rivers et al. [27] showed a 16% absolute risk mortality reduction. However, this result was subsequently challenged by multicenter randomized trials [8]. Monitoring of ScvO₂ has also shown to be useful to predict mortality in septic patients in the ED. In 619 patients visiting the ED with septic shock and who were treated according to EGDT protocol, Pope et al. reported an increased mortality in patients with ScvO₂ > 90% over the first 6 h of EGDT treatment (the so-called hyperoxia) [10]. By multivariate analysis, initial ScvO₂ < 70% was associated with mortality (OR 2.0, 95% CI 1.0–4.0). Over the first 6 h, both ScvO₂ < 70% and ScvO₂ > 90% were associated with higher mortality (OR 2.0, 95% CI 1.1–3.6 and OR 2.2, 95% CI 1.3–3.7, respectively). The authors hypothesized that hyperoxia, which describes a drop in oxygen delivery, and may be caused by the inability of cells to extract oxygen due to mitochondrial dysfunction and microcirculatory impairment in sepsis, may present even higher risks than hypoxia. In our study, the smaller size of our sample did not permit us to report on the prognostic impact of ScvO₂ > 90%.

In the present study, ScvO₂ was not used as a dynamic tool to guide resuscitation nor it was monitored during the first 6 h. Instead, it was used as a static one-shot parameter to assess outcomes and guide early patient management and hospital triage. Similarly, several studies have investigated the association between initial ScvO₂ value and outcomes of patients admitted to ICU with severe sepsis or septic shock with varying results. In 363 patients with septic shock, Boulain et al. showed that low ScvO₂ values on ICU admission (i.e., below 70%) were associated with higher mortality rates by day 28 (37.8% vs. 27.4%, respectively, $P=0.0049$), and that this association remained significant when adjusted for confounders (OR=3.60, 95% CI 1.76–7.36; $P=0.0004$) [9]. Similarly, Bracht et al. reported higher mortality rates in patients with ScvO₂ < 60% [28]. Conversely, in a smaller study with 52 septic shock patients with multiple organ dysfunction, Sasko et al. failed to demonstrate any association between ScvO₂ and day-28 mortality [29].

The prognostic impact of ScvO₂ in patients with febrile neutropenia deserves further investigation. In a prospective cohort of 547 patients with febrile neutropenia, Mato et al. showed that patients who developed septic shock within 48 h of a febrile neutropenia episode, frequently presented elevated levels of serum lactate (> 2 mmol/L) and tachypnea (> 20) [30]. Further studies are needed on such high-risk ED patients to assess workable clinical markers and biomarkers that can support risk stratification and optimize patient management and referral.

In the present study, 12% of patients met the outcome, which was independently associated with a poor performance status or a shock-index > 1. The shock index has been widely studied in ED patients, and was associated with a day 30 mortality when > 1 in a study by Kristensen et al. (111,019 ED patients, OR 10.5, 95% CI 9.3–11.7) [16]. The shock-index is easily accessible at triage, and may alert clinicians sooner in the early phases of sepsis [17].

Limits

This study evaluated only cancer patients with long-term CVCs. Nevertheless, the fraction of cancer patients with long-term CVCs is high [31].

The study sample included cancer patients with CVCs visiting the ED for various conditions, and not only infected patients. This heterogeneity in our population may have masked potential associations between ScvO₂ and the outcome.

The position of the CVC tip was not routinely assessed using chest X-ray. ScvO₂ is a surrogate marker of mixed venous oxygen saturation (SvO₂) that needs pulmonary artery catheterization. Both ScvO₂ and SvO₂ measurements may vary according to patient conditions (sepsis, cardiogenic shock) and to the placement of the CVC tip [32]. The choice of a 7 day outcome was somewhat arbitrary, and may seem ambitious for a triage tool in the ED. However, it is important to notice that, for the 25 patients that met the outcome, ICU admission or death occurred in the first 3 days for 23 and at day 4 and 5 for 2 of them.

In summary, ScvO₂ concentrations in ED patients with onco-hematological malignancies and long-term CVCs are not associated with ICU admission or death by day 7.

Author contributions OP, GD, JPF and EA made the study concept and design; OP, LL, AP, JF, MS, AV, JA, HM, AB, AG acquired the data; OP analyzed and interpreted the data; OP, JPF and EA drafted the manuscript; LL, AP, JF, MS, AV, JA, HM, AB, AG, MRR, JPF and EA made critical revision of the manuscript for important intellectual content; MRR gave statistical expertise.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights The study was approved by the regional Ethics Committee.

Informed consent Informed consent was obtained from all individual participants included in this study.

References

- Taboulet P, Moreira V, Haas L, Porcher R, Braganca A, Fontaine JP, Poncet MC (2009) Triage with the French Emergency Nurses Classification in Hospital scale: reliability and validity. *Eur J Emerg Med* 16:61–67
- Rady MY, Smithline HA, Blake H, Nowak R, Rivers E (1994) A comparison of the shock index and conventional vital signs to identify acute, critical illness in the emergency department. *Ann Emerg Med* 24:685–690
- Ait-Oufella H, Lemoine S, Boelle PY, Galbois A, Baudel JL, Lemant J, Joffre J, Margetis D, Guidet B, Maury E, Offenstadt G (2011) Mottling score predicts survival in septic shock. *Intensive Care Med* 37:801–807
- Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, Weiss JW (2005) Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 45:524–528
- Bloos F, Reinhart K (2005) Venous oximetry. *Intensive Care Med* 31:911e3
- van Beest P, Wietasch G, Scheeren T, Spronk P, Kuiper M (2011) Clinical review: use of venous oxygen saturations as a goal—a yet unfinished puzzle. *Crit Care* 15:232
- Hartog C, Bloos F (2014) Venous oxygen saturation. *Best Pract Res Clin Anaesthesiol* 28:419–428
- Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ, Davies A, Delaney A, Harrison DA, Holdgate A, Howe B, Huang DT, Iwashyna T, Kellum JA, Peake SL, Pike F, Reade MC, Rowan KM, Singer M, Webb SA, Weissfeld LA, Yealy DM, Young JD (2015) A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISE Investigators. *Intensive Care Med* 41:1549–1560
- Boulain T, Garot D, Vignon P, Lascarrou JB, Desachy A, Botoc V, Follin A, Frat JP, Bellec F, Quenot JP, Mathonnet A, Dequin PF (2014) Clinical Research in Intensive Care and Sepsis Group: prevalence of low central venous oxygen saturation in the first hours of intensive care unit admission and associated mortality in septic shock patients: a prospective multicentre study. *Crit Care* 18:609
- Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI (2010) Emergency Medicine Shock Research Network (EMShockNet) Investigators: multicenter study of central venous oxygen saturation (ScvO₂) as a predictor of mortality in patients with sepsis. *Ann Emerg Med* 55:40–46
- Mazzone A, Dentali F, La Regina M, Foglia E, Gambacorta M, Garagiola E, Bonardi G, Clerici P, Concia E, Colombo F, Campanini M (2016) Clinical features, short-term mortality, and prognostic risk factors of septic patients admitted to internal medicine units: results of an Italian Multicenter Prospective Study. *Medicine* 95:e2124
- Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, Lemeshow S, Osborn T, Terry KM, Levy MM (2017) Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* 376:2235–2244
- Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC (2016) Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 315:762–774
- Singer AJ, Ng J, Thode HC Jr, Spiegel R, Weingart S (2017) Quick SOFA scores predict mortality in adult emergency department patients with and without suspected infection. *Ann Emerg Med* 69:475–479
- Freund Y, Lemachatti N, Krastinova E, Van Laer M, Claesens YE, Avondo A, Occelli C, Feral-Pierssens AL, Truchot J, Ortega M, Carneiro B, Pernet J, Claret PG, Dami F, Bloom B, Riou B, Beaune S, French Society of Emergency Medicine Collaborators Group (2017) Prognostic accuracy of Sepsis-3 criteria for in-hospital mortality among patients with suspected infection presenting to the emergency department. *JAMA* 317:301–308
- Kristensen AK, Holler JG, Hallas J, Lassen A, Shapiro NI (2016) Is shock index a valid predictor of mortality in emergency department patients with hypertension, diabetes, high age, or receipt of β - or calcium channel blockers? *Ann Emerg Med* 67:106–113
- Berger T, Green J, Horeczko T, Hagar Y, Garg N, Suarez A, Panacek E, Shapiro N (2013) Shock index and early recognition of sepsis in the emergency department: pilot study. *West J Emerg Med* 14:168–174
- Park YJ, Kim DH, Kim SC, Kim TY, Kang C, Lee SH, Jeong JH, Lee SB, Lim D (2018) Serum lactate upon emergency department arrival as a predictor of 30-day in-hospital mortality in an unselected population. *PLoS One* 13:e0190519
- Shetty AL, Thompson K, Byth K, Macaskill P, Green M, Fullick M, Lander H, Iredell J (2018) Serum lactate cut-offs as a risk stratification tool for in-hospital adverse outcomes in emergency department patients screened for suspected sepsis. *BMJ Open* 8:e015492
- Rodriguez RM, Greenwood JC, Nuckton TJ, Darger B, Shofer FS, Troeger D, Jung SY, Speich KG, Valencia J, Kilgannon JH, Fernandez D, Baumann BM (2018) Comparison of qSOFA with current emergency department tools for screening of patients with sepsis for critical illness. *Emerg Med J* 35(6):350–356. <https://doi.org/10.1136/emered-2017-207383>
- Ouchi K, Hohmann S, Goto T, Ueda P, Aaronson EL, Pallin DJ, Testa MA, Tulskey JA, Schuur JD, Schonberg MA (2017) Index to predict in-hospital mortality in older adults after non-traumatic emergency department intubations. *West J Emerg Med* 18:690–697
- Moore JX, Akinyemiju T, Bartolucci A, Wang HE, Waterbor J, Griffin R (2018) A prospective study of cancer survivors and risk of sepsis within the REGARDS cohort. *Cancer Epidemiol* 55:30–38
- Brown J, Grudzen C, Kyriacou DN, Obermeyer Z, Quest T, Rivera D, Stone S, Wright J, Shelburne N (2016) The emergency care of patients with cancer: setting the research agenda. *Ann Emerg Med* 68:706–711
- Greene J (2015) CONCERN for cancer: new National Institutes of Health network to focus on cancer patients in the emergency department. *Ann Emerg Med* 66:13A–15A
- Boehm K, Duckheim M, Mizera L, Grogga-Bada P, Malek N, Kreth F, Gawaz M, Zuern CS, Eick C (2018) Heart rate variability for rapid risk stratification of emergency patients with malignant disease. *Support Care Cancer* 26:3289–3296
- Coyne CJ, Le V, Brennan JJ, Castillo EM, Shatsky RA, Ferran K, Brodine S, Vilke GM (2017) Application of the MASCC and CISNE risk-stratification scores to identify low-risk febrile

- neutropenic patients in the emergency department. *Ann Emerg Med* 69:755–764
27. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345:1368–1377
 28. Bracht H, Hänggi M, Jeker B, Wegmüller N, Porta F, Tüller D, Takala J, Jakob SM (2007) Incidence of low central venous oxygen saturation during unplanned admissions in a multidisciplinary intensive care unit: an observational study. *Crit Care* 11:R2
 29. Sasko B, Butz T, Prull MW, Liebeton J, Christ M, Trappe HJ (2015) Earliest bedside assessment of hemodynamic parameters and cardiac biomarkers: their role as predictors of adverse outcome in patients with septic shock. *Int J Med Sci* 12:680–688
 30. Mato AR, Luger SM, Heitjan DF, Mikkelsen ME, Olson E, Ujjani C, Jacobs S, Miltiades AN, Shah P, Schuster SJ, Carroll M, Chauffe AD, Fuchs BD (2010) Elevation in serum lactate at the time of febrile neutropenia (FN) in hemodynamically-stable patients with hematologic malignancies (HM) is associated with the development of septic shock within 48 hours. *Cancer Biol Ther* 9:585–589
 31. Schiffer CA, Mangu PB, Wade JC, Camp-Sorrell D, Cope DG, El-Rayes BF, Gorman M, Ligibel J, Mansfield P, Levine M (2013) Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 31:1357–1370
 32. Kopterides P, Bonovas S, Mavrou I, Kostadima E, Zakyntinos E, Armaganidis A (2009) Venous oxygen saturation and lactate gradient from superior vena cava to pulmonary artery in patients with septic shock. *Shock* 31:561–567