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Narrative review: clinical assessment of peripheral tissue perfusion in septic shock

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Abstract

Sepsis is one of the main reasons for intensive care unit admission and is responsible for high morbidity and mortality. The usual hemodynamic targets for resuscitation of patients with septic shock use macro-hemodynamic parameters (hearth rate, mean arterial pressure, central venous pressure). However, persistent alterations of microcirculatory blood flow despite restoration of macro-hemodynamic parameters can lead to organ failure. This dissociation between macro- and microcirculatory compartments brings a need to assess end organs tissue perfusion in patients with septic shock. Traditional markers of tissue perfusion may not be readily available (lactate) or may take time to assess (urine output). The skin, an easily accessible organ, allows clinicians to quickly evaluate the peripheral tissue perfusion with noninvasive bedside parameters such as the skin temperatures gradient, the capillary refill time, the extent of mottling and the peripheral perfusion index.

Keywords: Septic shock, Microcirculation, Capillary refill time, Temperatures gradient, Peripheral perfusion index, Mottling, Skin

Background

International guidelines emphasized that fast identification, assessment and treatment combining early antibiotic therapy, fluid administration and vasopressor infusion are crucial steps in the management of septic shock. However, despite early management, mortality of patients with septic shock remains high [1]. A possible explanation may be the persistent tissue hypoperfusion despite restoration of macro-hemodynamic parameters.

The usual hemodynamic targets for resuscitation of patients with septic shock use macro-hemodynamic parameters (heart rate, mean arterial pressure, central venous pressure). However, persistent alterations of microcirculatory blood flow despite restoration of macro-hemodynamic parameters can lead to organ failure. In a meta-analysis of 252 patients, De Backer et al. [2] showed that microcirculatory perfusion alterations predict mortality during serious infections, whereas mean arterial pressure or cardiac output did not. In critically ill patients, cardiac output optimization using increasing doses of dobutamine did not improve microvascular blood flow in the sublingual area [3, 4]. In another study, modulating mean arterial pressure by increasing norepinephrine dose had variable unpredictable effects on microcirculatory flow, which occasionally worsened [5, 6]. This dissociation between macro- and microcirculatory compartments, defined by Ince as «a loss of hemodynamic coherence» [7], brings a need to assess end organs tissue perfusion in patients with septic shock and to develop tools to analyze microcirculatory blood flow [8]. The direct identification of severe microcirculatory alterations remains difficult at bedside. Traditional markers of tissue perfusion may not be readily available (lactate) or may take time to assess (urine output). The skin, an easily accessible organ, allows clinicians to quickly evaluate the peripheral tissue perfusion with noninvasive bedside parameters such as the skin temperatures gradient, the capillary refill time, the extent of mottling and the peripheral perfusion index.

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The aim of this review is to evaluate whether peripheral tissue perfusion assessment in septic patients could be helpful in evaluating organ failure severity and to screen patients at high risk of mortality. Finally, we analyze available data regarding implementation of peripheral perfusion evaluation in sepsis management.

Skin as a tool for the evaluation of the microcirculation and tissue perfusion

The skin provides important information in patients with septic shock. As a visible and easily accessible organ, the skin allows simple observation of local microcirculatory perfusion through skin temperature alterations (skin temperature gradient), perfusion (capillary refill time) and color (mottling). The pathophysiology of these clinical disorders has not been investigated in depth, but several authors assume that the main driven mechanism of reduced blood flow is local vasoconstriction mediated by sympathetic neuroactivation [8]. Additional mechanisms could participate to impair microvascular blood flow (Fig. 1) [9, 10] such as local endothelial dysfunction [11, 12] (Fig. 2), leukocyte adhesion, platelet activation and fibrin deposition [13]. These clinical, noninvasive, easy-to-use, parameters are attractive tools to follow microcirculatory perfusion in patients with acute circulatory failure [14, 15]. In 2014, several European experts recommended to integrate abnormal skin perfusion parameters in the definition and treatment of shock [16].

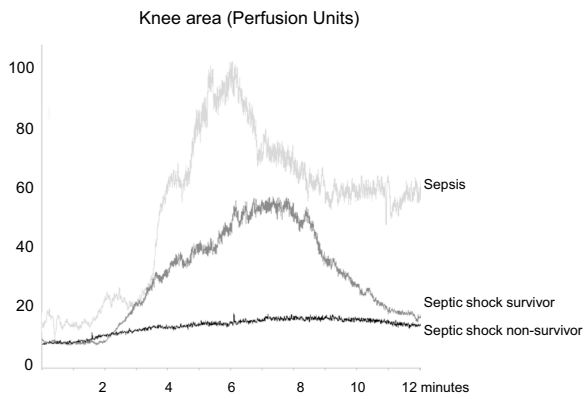

Fig. 2 Examples of skin microcirculatory endothelial reactivity in the knee area in a patients with sepsis, in a patient with septic shock that was alive at day 14 and in a patient with septic shock that was ultimately dead at day 14. Skin microcirculatory blood flow was measured at baseline and after acetylcholine iontophoresis. Adapted from [11]

Subjective assessment of peripheral skin temperature may be a valuable tool in the evaluation of patients with septic shock. Eighty years ago, Ebert et al. [17] described the skin of septic shock patients as being «pale, often sweaty». Altemeier et al. [18] then noticed that a moist and cold skin was a factor of worse prognosis in patients with septic shock. Cold hands and feet, and abnormal skin color are the first clinical signs that developed

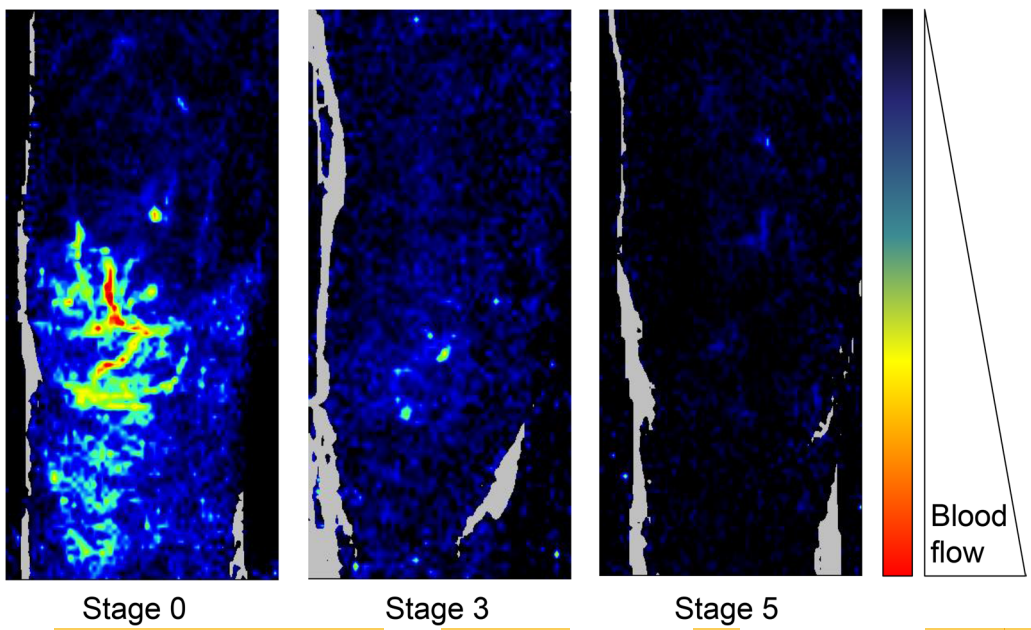

Fig. 1 Examples of skin microvascular perfusion evaluation using laser Doppler imaging in the knee area according to the mottling score. Skin perfusion decreases when mottling score worsens. Adapted from [9]

in meningococcal disease in children [19]. In a cohort of 264 surgical ICU patients, patients with cold skin on extremities and knees had significantly lower central venous saturation and higher lactate level as compared to patients with normal skin temperature (4.7 ± 1.5 vs 2.2 ± 1.6 mmol/L, $p < 0.05$) [20]. In a prospective cohort study of 50 critically ill patients with circulatory dysfunction, including 26 patients with septic shock, Lima et al. [21] observed that patients with cold skin on the extremities had a higher rate of organ failure at 48 h after resuscitation as compared to patients with normal skin temperature.

However, skin temperature gradients may be more accurate in the evaluation of patients with septic shock. Several studies investigated quantitative temperature gradients in critically ill patients, particularly between peripheral and ambient temperatures [22], central and peripheral body temperatures [23] and finger and forearm skin temperatures [24]. Temperature gradients do not correlate with cardiac output [22, 25, 26] but are predictive of both organ failure severity and worse outcome. Joly et al. [22] measured toe-to-ambient temperature gradients 3 h after admission in a mixed population of critically ill patients, and non-survivors had a mean toe-ambient temperature gradient of 0.9 °C, whereas survivors had a gradient of 3.4 °C. Normalization of central-peripheral temperature gradients (< 7 °C) within the 6 first hours of resuscitation predicted correction of hyperlactatemia in septic shock patients [27]. In a recent study including 103 septic patients, Bourcier et al. [28] reported higher central-to-toe temperature gradients and lower toe-to-ambient temperature gradients in patients with septic shock, compared to patients with sepsis. Moreover, a rise in the toe-to-ambient temperature gradient was independently associated with decreased ICU mortality (OR 0.7 [0.5, 0.9] per °C, $p < 0.001$).

Finger-to-forearm skin and toe-to-ambient temperature gradients are more accurate tools that could be used in every patient without previous hypothermia, including patients with dark skin, providing quantitative information with good reproducibility (Table 1, Fig. 3).

Capillary refill time

The capillary refill time (CRT) measures the amount of time necessary for the skin to return to baseline color after applying a pressure on a soft tissue (generally finger tip). The CRT gives important information on skin perfusion and microcirculatory status but does not reflect cardiac output [25, 29]. Visual measurement of CRT associated with other clinical signs (tachycardia, mucosal dryness, etc.) helps to diagnose dehydration in children [30]. In acute pathologies, such as gastro-intestinal infections or malaria [31], CRT represents an attractive and easy-to-use tool for clinicians in the initial screening of severely ill patients [32]. Inter-rater variability of CRT was weak in non-trained physicians [33], but is better in centers expert in tissue perfusion evaluation [34], especially in the knee area [35]. Standardization of finger-tip pressure (i.e., How long? How strong the applied pressure?) might improve CRT reproducibility. Ait-Oufella et al. [35] obtained good inter-rater concordance by "applying a firm pressure for 15 s. The pressure applied was just enough to remove the blood at the finger tip of the physician's nail illustrated by appearance of a thin white distal crescent (blanching) under the nail."

Capillary refill time measurement correlates with the pulsatility index, a surrogate ultrasound-derived parameter that reflects vascular tone of visceral organs in septic shock patients [36]. CRT is an interesting tool to assess the severity of an acute illness. In the intensive care unit, Lima et al. [21] reported an association between a prolonged CRT (> 4.5 s on the index finger) and hyperlactatemia and a higher SOFA score. In septic shock patients, a prolonged CRT 6 h after resuscitation has been shown to be predictive of 14-day mortality, with an Area Under Curve (AUC) of 84% for a measure on the index finger, and 90% for a measure on the knee. A 2.4-second threshold value on the index finger predicted mortality with an 82% sensitivity (95% CI [60–95]) and a 73% specificity (95% CI [56–86]). On the knee, a threshold value of 4.9 s predicted 14-day mortality with an 82% sensitivity (95% CI [60–95]) and an 84% specificity (95% CI [68–94]) [35].

Overall, when used as a qualitative variable (prolonged or not), CRT is a reliable triage tool to identify critically ill patients at risk of negative outcome. Quantitative measurement of CRT should be mainly used by trained physicians in patients with non-dark skin (Table 1, Fig. 3).

Mottling

Mottling, a characteristic discoloration of the skin following reduced skin blood flow [9], is taught as a marker of shock, but its clinical relevance has been poorly investigated until recent years. A significant relationship between mottling extension and visceral organ vascular tone has been reported suggesting that mottling could reflect gut, liver spleen and kidney hypoperfusion [36].

To assess the predictive value of mottling in critically ill patients with severe infections, a semi-quantitative clinical score for mottling (ranging from 0 to 5), based on the extension of these purple patches from the patella toward the periphery, has been developed and validated with an excellent inter-observer reproducibility [37] (Kappa 0.87% (CI 95% [0.72–0.97]) (Fig. 4). Mottling score reliably reflects organ failure severity in patients with sepsis or septic shock and helps to

Table 1 Summary of selected studies investigating clinical parameters of peripheral tissue in critically ill sepsis patients

Parameters	References	Patients' number	% sepsis	% septic shock	Relation to organ failure severity	Relation to mortality	Changes following resuscitation
Peripheral temperature							
Subjective assessment: cold versus warm extremities	Kaplan et al. [20]	264	42	–	Cold extremities group had lower cardiac index, lower SvO2 and higher lactate levels	–	–
Toe-to-room temperature gradient	Joly et al. [22]	100	20			Temperature gradient lower in non-survivors	Temperature gradient increased in non-survivors following resuscitation but decreased in non-survivors
Toe-to-room temperature gradient	Bourcier et al. [28]	103	39	61	–	Lower in MOF death patients	Decreased in MOF death patients but increased in survivors
Capillary refill time (CRT)							
Finger-tip and knee CRT	Ait-Oufella et al. [35]	59	0	100	Correlated with SOFA score	Related to Day-14 mortality	CRT decreased during resuscitation which is associated with better outcome
Finger-tip CRT	Lara et al. [47]	95	100	–	–	–	Prolonged CRT following resuscitation is associated with higher organ failure severity and higher mortality
Finger-tip CRT	Hernandez et al. [46]	104	0	100	–	–	CRT is normalized within 6 h following resuscitation, whereas lactate normalization is longer
Mottling							
Mottling score after initial resuscitation	Ait-Oufella et al. [37]	60	0	100	Correlated with lactate, urinary output and SOFA score	Related to Day-14 mortality	Mottling score decreased following resuscitation which was associated with better outcome
	De Moura et al. [39]	97	0	100	–	Related to Day-28 mortality	–
	Preda et al. [41]	109	100	0	–	Related to Day-28 mortality	–
Mottling presence	Coudroy et al. [40]	791	–	–	–	Related to Day-28 mortality	Mottling persistence > 6 h was associated with higher mortality
Combined parameters							
Finger tip CRT + temperature gradient + peripheral perfusion index	Lima et al. [21]	50	–	42	Associated with lactate levels	–	Peripheral hypoperfusion associated with worsening SOFA score following resuscitation
CRT and central-to-toe temperature gradient	Hernandez et al. [27]	41	33	67	–	–	CRT is the first be normalized during resuscitation within 2 h

CRT capillary refill time, *MOF* multiorgan failure, *SOFA* sequential organ failure assessment

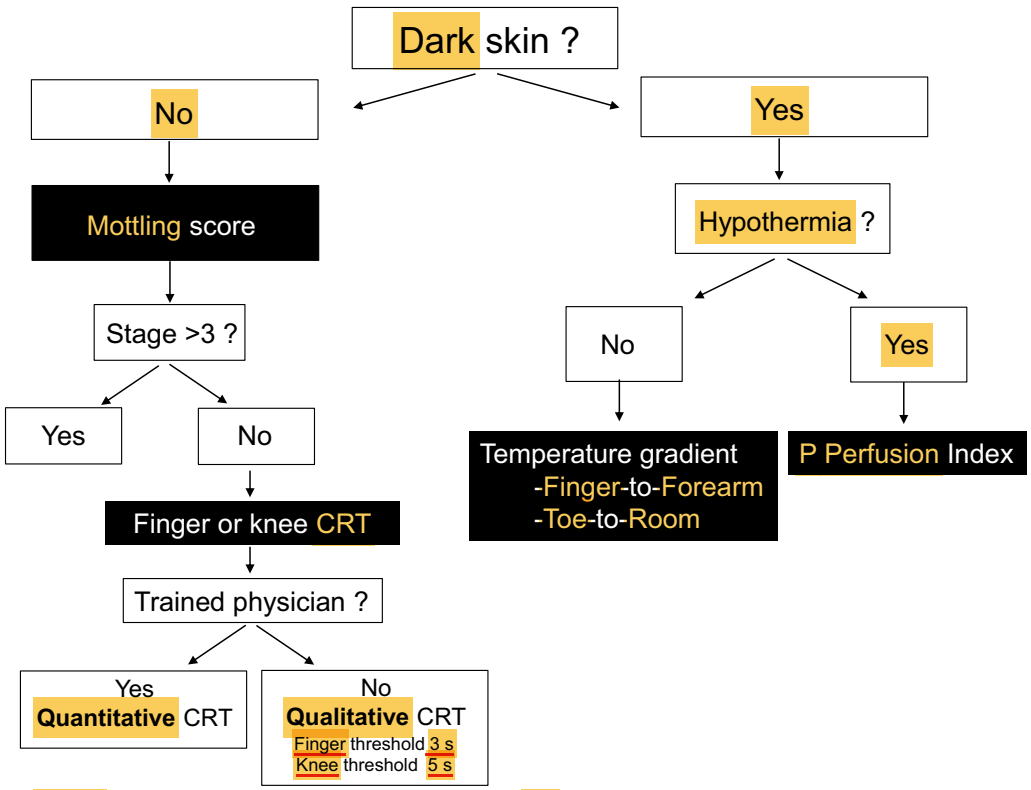

Fig. 3 Proposed strategy to evaluate peripheral tissue perfusion using the skin. *CRT* capillary refill time, *P.Perfusion index* peripheral perfusion index

identify critically ill patients with worse outcome. In a study including septic shock patients, the mottling score at 6 h after resuscitation was predictive of death at day 14 (odds radio [OR] 16, CI 95% 4–81, for stages 2–3; vs 74, CI 95% 11–1568, for stages 4–5). Mortality occurred within 12–24 h for stages 4–5, within 24–72 h for stages 2–3 and later than 72 h for the rare deaths for stages 0–1 (Kaplan–Meier charts, $p < 0.0001$). In the same study, cardiac output and blood pressure were not associated with mortality at day 14, confirming the disparity between microcirculatory and macrocirculatory parameters [37]. These results were confirmed in cirrhotic patients with septic shock [38]. In addition, in mottling groups ≤ 3, knee CRT improved patient discrimination according to their outcome, with non-survivors presenting a significantly higher knee CRT [35]. Another South American study confirmed these results in septic shock patients. Mortality rate at day 28 was 100% when the mottling score was higher or equal to stage 4, 77% for stages 2 and 3, and 45% for stages 1 or lower [39]. Prognostic value of mottling was also reported in unselected ICU patients: Persistent (> 6 h) mottling extending over the knee (> stage 2) was an independent risk factor for mortality (OR 3.29, 95% CI 2.08–5.19; $p < 0.0001$) [40]. Finally, Preda et al. [41] found the good predictive value of the mottling score for mortality at day 28 in patients with sepsis not receiving vasopressors.

In summary, mottling score is a reliable semi-quantitative tool that reflects organ failure severity in non-selected septic patients with or without vasopressors and is helpful to identify critically ill patients with pejorative outcome and also to monitor changes during resuscitation. In patients with mottling score ranging from 0 to 3, knee CRT measurement could be associated with improving risk stratification (Table 1, Fig. 3).

Peripheral perfusion index

Peripheral perfusion index is defined as the difference between the pulsatile and non-pulsatile portion of pulse wave, measured by plethysmography. Peripheral perfusion index (PPI) gives information on peripheral vascular tonus by the pulsatility, decreasing in vasoconstriction and raising in vasodilation [42]. Peripheral perfusion index is an early predictor of central hypovolemia [43]. In a prospective observational study in an emergency department, PPI was not significantly different between patients admitted to the hospital and patients discharged from the emergency department suggesting that it could not be used as a triage tool [44]. However, in critically

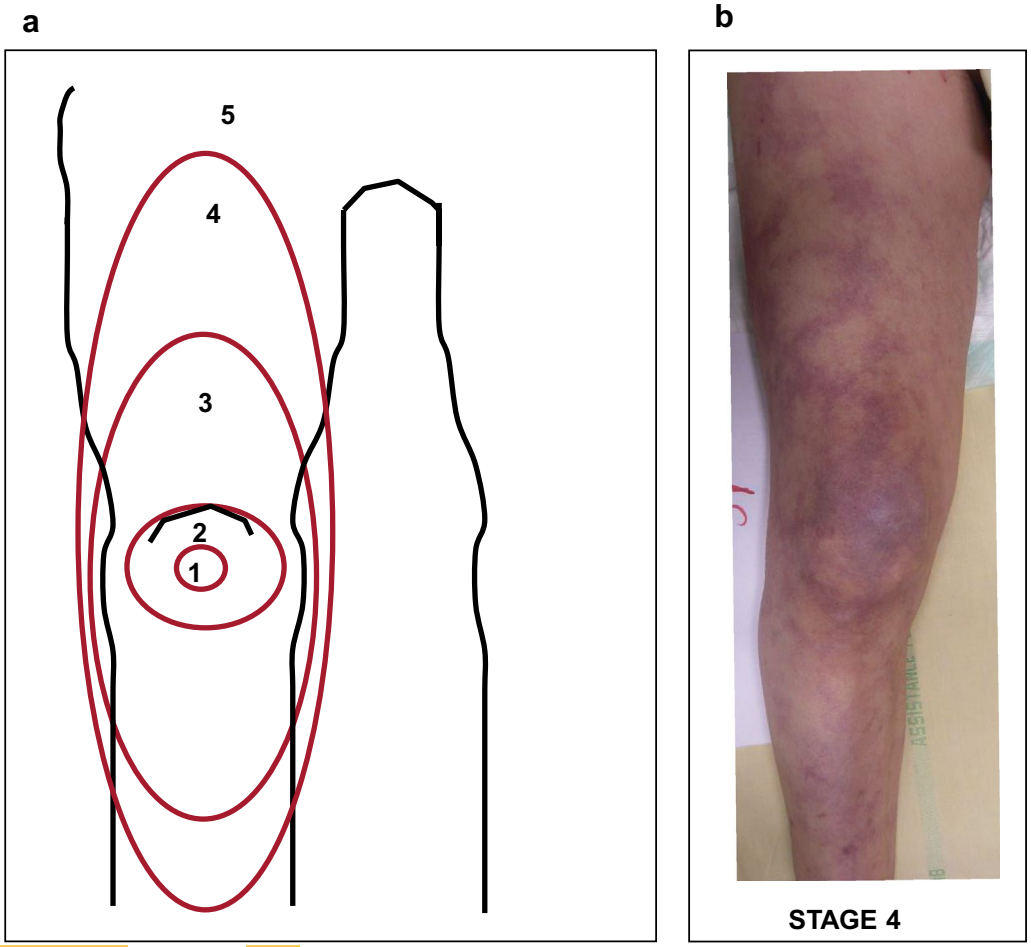

Fig. 4 **a** The mottling score, ranging from 0 to 5, is based on skin mottling area extension on legs. Score 0 represents no mottling, score 1 represents small mottling area (coin size) localized to the center of the knee, score 2 represents mottling area not exceeding the superior edge of the knee cap, score 3 represents mottling area not exceeding the middle thigh, score 4 represents mottling area not exceeding the fold of the groin and score 5 otherwise. **b** Example of mottling score 5. Adapted from [37]

ill patients, PPI is significantly lower in patients with a peripheral perfusion alteration (0.7 vs 2.3, $p<0.01$) [21]. He et al. [45] showed that the PPI is altered in septic shock patients, as compared to control subjects in postoperative scheduled surgery. Moreover, in the same study, the PPI was significantly lower in non-survivors. With a 0.20 cutoff value, PPI was predictive of ICU mortality with an AUC of 84% (69–96), a sensitivity of 65% and a specificity of 92%.

Discussion

Abnormal skin perfusion evaluation and resuscitation

Despite some differences between micro and macrovascular compartments, it would be over-simplifying and possibly wrong to completely separate these two vascular compartments. In the study by Ait-Oufella et al. [37] focusing on mottling, global hemodynamic improvement within the first hours following resuscitation, based on blood volume optimization and catecholamine use, was associated with mottling improvement. Patients whose mottling score improved through the first 6-hour resuscitation had a good prognosis, whereas those whose score was stable or even worsened had a poor prognosis (14-day mortality: 23% vs 88%, $p<0.001$). Finger-tip CRT is also quickly normalized in septic shock patients within 2–6 h after resuscitation, whereas hyperlactatemia requires longer time to recover [27, 46]. Interestingly, patients in whom CRT did not recover after fluid infusion had pejorative outcome [47]. Altogether, these studies suggest that peripheral tissue perfusion could be used as triage tool at the early steps of sepsis management at admission and after fluid infusion. The ongoing ANDROMEDA-SHOCK trial aims to compare two resuscitation strategies during the first hours of sepsis

treatment on 28-day mortality, one based on CRT measurement and the other on arterial lactate clearance [48]. During ICU stay, evaluation of peripheral perfusion could also be helpful. A «proof-of-concept» study has been done comparing a volume expansion strategy based on peripheral perfusion, clinical parameter assessment, to a classical strategy based on mean arterial pressure, central venous pressure and cardiac index. Peripheral perfusion was assessed through CRT, index-forearm temperature gradient, peripheral perfusion index, and StO2. The resuscitation strategy based on clinical tissue perfusion assessment led to a reduction in fluid therapy volume in the first 72 h (7565 ± 982 mL vs. 10,028 ± 941 mL, $p = 0.08$) and to a reduction in hospital length of stay (16 [5–28] vs. 43 [8–45] days, $p < 0.05$) [49]. A task force of six international experts with extensive bedside experience recently proposed to integrate peripheral tissue perfusion tools in risk stratification and management of septic patients in resource-limited intensive care units, especially CRT, mottling score and temperature gradients [50].

As bedside evaluation of tissue perfusion using the skin improves risk stratification in patients with sepsis, there is a possibility that it could be used as a tool to guide resuscitation. Lavillegrand et al. [51] reported that a mild arterial hypotension (MAP between 55 and 65 mmHg) could be safely tolerated in patients without any sign of hypoperfusion. Such «personalized» management requires close monitoring (in an ICU) but may decrease the use of invasive devices and vasopressors, both having potential side effects. Conversely, patients with markers of tissue hypoperfusion require rapid ICU transfer, and also, we hypothesized that they should be good candidate for therapeutic approaches targeting microcirculation for resuscitation in the future. For example, nitroglycerin infusion had no beneficial effect in unselected sepsis patients [52] but improved peripheral perfusion in selected patients with prolonged CRT and/or increased finger-tip-to-forearm skin gradient temperatures [53]. Ilomedin has been also recently proposed as a rescue therapy in sepsis shock with refractory tissue hypoperfusion [54] and will be tested soon in a prospective randomized multicenter trial (I-MICRO NCT03788837). In the future, it is important to evaluate whether drugs targeting the microcirculation could improve outcome of selected patients with persistent peripheral hypoperfusion despite initial resuscitation [55]. The first results of ANDROMEDA-SHOCK, an international multicenter trial recently completed, support that a tissue perfusion-guided resuscitation is beneficial [48, 56]. Indeed, Hernandez et al. [56] showed in septic shock adults that an early peripheral perfusion-targeted resuscitation, aiming at normalizing capillary refill time, was associated with less organ dysfunction at day 3 and a trend toward reduced 28-day mortality when compared to a lactate-level-targeted therapeutic strategy.

Limitations

In this review, almost all data were obtained in small-sized monocenter observational studies and were performed by experts in tissue perfusion evaluation, suggesting potential biases. In addition, no published multicenter randomized trial is available showing that the implementation of bedside tissue perfusion assessment improves septic patients management and *in fine* outcome. This narrative review did not provide strong recommendation regarding the use of tissue perfusion parameters in septic patients according to GRADE methodology but only proposed how and when to implement them.

Conclusion

In patients with septic shock, tissue microvascular hypoperfusion can be evaluated at bedside using indicators of skin perfusion. After initial resuscitation, these parameters are helpful in identifying patients with severe organ failure and at high risk of mortality. However, there is a need in the future to investigate these bedside tissue microvascular perfusion parameters as management targets for resuscitation in septic shock patients.

Abbreviations

CI: confidence interval; CRT: capillary refill time; ICU: intensive care unit; MAP: mean arterial pressure; NIRS: near-infrared spectroscopy; NO: nitric oxide; OR: odds ratio; PPI: peripheral perfusion index; SOFA: sequential organ failure assessment; SAPS II: Simplified Acute Physiologic Score II; ROC: receiver operating characteristics.

Authors' contributions

Drafting and critical revision of manuscript was done by all authors. All authors read and approved the final manuscript.

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References

1. Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009–2014. JAMA. 2017;318(13):1241–9.
2. De Backer D, Donadello K, Sakr Y, Ospina-Tascon G, Salgado D, Scolletta S, et al. Microcirculatory alterations in patients with severe sepsis: impact of time of assessment and relationship with outcome. Crit Care Med. 2013;41(3):791–9.
3. De Backer D, Creteur J, Dubois MJ, Sakr Y, Koch M, Verdant C, et al. The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. Crit Care Med. 2006;34(2):403–8.
4. Hernandez G, Bruhn A, Luengo C, Regueira T, Kattan E, Fuentealba A, et al. Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study. Intensive Care Med. 2013;39(8):1435–43.
5. Dubin A, Pozo MO, Casabella CA, Palizas F Jr, Murias G, Moseinco MC, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. Crit Care. 2009;13(3):R92.
6. Thooft A, Favory R, Salgado DR, Taccone FS, Donadello K, De Backer D, et al. Effects of changes in arterial pressure on organ perfusion during septic shock. Crit Care. 2011;15(5):R222.
7. Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit Care. 2015;19(Suppl 3):S8.
8. Lima A, Bakker J. Noninvasive monitoring of peripheral perfusion. Intensive Care Med. 2005;31(10):1316–26.
9. Ait-Oufella H, Bourcier S, Alves M, Galbois A, Baudel JL, Margetis D, et al. Alteration of skin perfusion in mottling area during septic shock. Ann Intensive Care. 2013;3(1):31.
10. Ait-Oufella H, Bourcier S, Lehoux S, Guidet B. Microcirculatory disorders during septic shock. Curr Opin Crit Care. 2015;21(4):271–5.
11. Bourcier S, Joffre J, Dubee V, Preda G, Baudel JL, Bige N, et al. Marked regional endothelial dysfunction in mottled skin area in patients with severe infections. Crit Care. 2017;21(1):155.
12. Becker L, Prado K, Foppa M, Martinelli N, Aguiar C, Furian T, et al. Endothelial dysfunction assessed by brachial artery ultrasound in severe sepsis and septic shock. J Crit Care. 2012;27(3):316e9–14.
13. Ait-Oufella H, Maury E, Lehoux S, Guidet B, Offenstadt G. The endothelium: physiological functions and role in microcirculatory failure during severe sepsis. Intensive Care Med. 2010;36(8):1286–98.
14. Ait-Oufella H, Bakker J. Understanding clinical signs of poor tissue perfusion during septic shock. Intensive Care Med. 2016;42(12):2070–2.
15. Lima A, Bakker J. Clinical assessment of peripheral circulation. Curr Opin Crit Care. 2015;21(3):226–31.
16. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40(12):1795–815.
17. Ebert RV, Stead EA. Circulatory failure in acute infections. J Clin Invest. 1941;20(6):671–9.
18. Altemeier WA, Cole W. Septic shock. Ann Surg. 1956;143(5):600–7.
19. Thompson MJ, Ninis N, Perera R, Mayon-White R, Phillips C, Bailey L, et al. Clinical recognition of meningococcal disease in children and adolescents. Lancet. 2006;367(9508):397–403.
20. Kaplan LJ, McPartland K, Santora TA, Trooskin SZ. Start with a subjective assessment of skin temperature to identify hypoperfusion in intensive care unit patients. J Trauma. 2001;50(4):620–7 **(discussion 7–8)**.
21. Lima A, Jansen TC, van Bommel J, Ince C, Bakker J. The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients. Crit Care Med. 2009;37(3):934–8.
22. Joly HR, Weil MH. Temperature of the great toe as an indication of the severity of shock. Circulation. 1969;39(1):131–8.
23. Ibsen B. Treatment of shock with vasodilators measuring skin temperature on the big toe. Ten years' experience in 150 cases. Dis Chest. 1967;52(4):425–9.
24. House JR, Tipton MJ. Using skin temperature gradients or skin heat flux measurements to determine thresholds of vasoconstriction and vasodilatation. Eur J Appl Physiol. 2002;88(1–2):141–5.
25. Bailey JM, Levy JH, Kopel MA, Tobia V, Grabenkort WR. Relationship between clinical evaluation of peripheral perfusion and global hemodynamics in adults after cardiac surgery. Crit Care Med. 1990;18(12):1353–6.
26. Vincent JL, Moraine JJ, van der Linden P. Toe temperature versus transcutaneous oxygen tension monitoring during acute circulatory failure. Intensive Care Med. 1988;14(1):64–8.
27. Hernandez G, Pedreros C, Veas E, Bruhn A, Romero C, Rovegno M, et al. Evolution of peripheral vs metabolic perfusion parameters during septic shock resuscitation.A clinical-physiologic study. J Crit Care. 2012;27(3):283–8.
28. Bourcier S, Pichereau C, Boelle PY, Nemlaghi S, Dubee V, Lejour G, et al. Toe-to-room temperature gradient correlates with tissue perfusion and predicts outcome in selected critically ill patients with severe infections. Ann Intensive Care. 2016;6(1):63.
29. Tibby SM, Hatherill M, Murdoch IA. Capillary refill and core-peripheral temperature gap as indicators of haemodynamic status in paediatric intensive care patients. Arch Dis Child. 1999;80(2):163–6.
30. Gorelick MH, Shaw KN, Murphy KO. Validity and reliability of clinical signs in the diagnosis of dehydration in children. Pediatrics. 1997;99(5):E6.
31. Evans JA, May J, Ansong D, Antwi S, Asafo-Adjei E, Nguah SB, et al. Capillary refill time as an independent prognostic indicator in severe and complicated malaria. J Pediatr. 2006;149(5):676–81.
32. Gove S, Tamburlini G, Molyneux E, Whitesell P, Campbell H. Development and technical basis of simplified guidelines for emergency triage assessment and treatment in developing countries. WHO Integrated Management of Childhood Illness (IMCI) Referral Care Project. Arch Dis Child. 1999;81(6):473–7.
33. Alsma J, van Saase J, Nanayakkara PWB, Schouten W, Baten A, Bauer MP, et al. The power of flash mob research: conducting a nationwide observational clinical study on capillary refill time in a single day. Chest. 2017;151(5):1106–13.
34. van Genderen ME, Paauwe J, de Jonge J, van der Valk RJ, Lima A, Bakker J, et al. Clinical assessment of peripheral perfusion to predict postoperative complications after major abdominal surgery early: a prospective observational study in adults. Crit Care. 2014;18(3):R114.
35. Ait-Oufella H, Bige N, Boelle PY, Pichereau C, Alves M, Bertinchamp R, et al. Capillary refill time exploration during septic shock. Intensive Care Med. 2014;40(7):958–64.
36. Brunauer A, Kokofer A, Bataar O, Gradwohl-Matis I, Dankl D, Bakker J, et al. Changes in peripheral perfusion relate to visceral organ perfusion in early septic shock: a pilot study. J Crit Care. 2016;35:105–9.
37. Ait-Oufella H, Lemoinne S, Boelle PY, Galbois A, Baudel JL, Lemant J, et al. Mottling score predicts survival in septic shock. Intensive Care Med. 2011;37(5):801–7.
38. Galbois A, Bige N, Pichereau C, Boelle PY, Baudel JL, Bourcier S, et al. Exploration of skin perfusion in cirrhotic patients with septic shock. J Hepatol. 2015;62(3):549–55.

39. de Moura EB, Amorim FF, da Cruz Santana AN, Kanhouche G, de Souza Godoy LG, de Jesus Almeida L, et al. Skin mottling score as a predictor of 28-day mortality in patients with septic shock. Intensive Care Med. 2016;42(3):479–80.
40. Coudroy R, Jamet A, Frat JP, Veinstein A, Chatellier D, Goudet V, et al. Incidence and impact of skin mottling over the knee and its duration on outcome in critically ill patients. Intensive Care Med. 2015;41(3):452–9.
41. Preda G, Bourcier S, Joffre J, Boelle PY, Dubee V, Baudel JL, et al. Mottling score is associated with 28-day mortality in critically ill patients with sepsis. Minerva Anestesiol. 2017;83(6):664–6.
42. Hales JR, Stephens FR, Fawcett AA, Daniel K, Sheahan J, Westerman RA, et al. Observations on a new non-invasive monitor of skin blood flow. Clin Exp Pharmacol Physiol. 1989;16(5):403–15.
43. van Genderen ME, Bartels SA, Lima A, Bezemer R, Ince C, Bakker J, et al. Peripheral perfusion index as an early predictor for central hypovolemia in awake healthy volunteers. Anesth Analg. 2013;116(2):351–6.
44. Oskay A, Eray O, Dinc SE, Aydin AG, Eken C. Prognosis of Critically ill patients in the ED and value of perfusion index measurement: a cross-sectional study. Am J Emerg Med. 2015;33(8):1042–4.
45. He HW, Liu DW, Long Y, Wang XT. The peripheral perfusion index and transcutaneous oxygen challenge test are predictive of mortality in septic patients after resuscitation. Crit Care. 2013;17(3):R116.
46. Hernandez G, Luengo C, Bruhn A, Kattan E, Friedman G, Ospina-Tascon GA, et al. When to stop septic shock resuscitation: clues from a dynamic perfusion monitoring. Ann Intensive Care. 2014;4:30.
47. Lara B, Enberg L, Ortega M, Leon P, Kripper C, Aguilera P, et al. Capillary refill time during fluid resuscitation in patients with sepsis-related hyperlactatemia at the emergency department is related to mortality. PLoS ONE. 2017;12(11):e0188548.
48. Hernandez G, Cavalcanti AB, Ospina-Tascon G, Zampieri FG, Dubin A, Hurtado FJ, et al. Early goal-directed therapy using a physiological holistic view: the ANDROMEDA-SHOCK—a randomized controlled trial. Ann Intensive Care. 2018;8(1):52.
49. van Genderen ME, Engels N, van der Valk RJ, Lima A, Klijn E, Bakker J, et al. Early peripheral perfusion-guided fluid therapy in patients with septic shock. Am J Respir Crit Care Med. 2015;191(4):477–80.
50. Misango D, Pattnaik R, Baker T, Dunser MW, Dondorp AM, Schultz MJ, et al. Haemodynamic assessment and support in sepsis and septic shock in resource-limited settings. Trans R Soc Trop Med Hyg. 2017;111(11):483–9.
51. Lavillegrand JR, Dumas G, Bige N, Zafimahazo D, Guidet B, Maury E, et al. Should we treat mild hypotension in septic patients in the absence of peripheral tissue hypoperfusion? Intensive Care Med. 2018;44(9):1593–4.
52. Boerma EC, Koopmans M, Konijn A, Kaiferova K, Bakker AJ, van Roon EN, et al. Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: a double-blind randomized placebo controlled trial. Crit Care Med. 2010;38(1):93–100.
53. Lima A, van Genderen ME, van Bommel J, Klijn E, Jansem T, Bakker J. Nitroglycerin reverts clinical manifestations of poor peripheral perfusion in patients with circulatory shock. Crit Care. 2014;18(3):R126.
54. Depret F, Sitbon A, Soussi S, De Tymowski C, Blet A, Fratani A, et al. Intravenous iloprost to recruit the microcirculation in septic shock patients? Intensive Care Med. 2018;44(1):121–2.
55. Legrand M, Ait-Oufella H, Ince C. Could resuscitation be based on microcirculation data? Yes. Intensive Care Med. 2018;44(6):944–6.
56. Hernandez G, Ospina-Tascon GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. JAMA. 2019;321(7):654–64.

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LETTER

Capillary refill time status could identify different clinical phenotypes among septic shock patients fulfilling Sepsis-3 criteria: a post hoc analysis of ANDROMEDA-SHOCK trial

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Dear Editor,

The Sepsis-3 definition of septic shock is used to create a subset of patients with suspected or proven infection having an homogeneous risk of death based on large databases (>40%) [1]. This definition has been criticized as hyperlactatemia is a non-specific marker of tissue hypo-perfusion. Therefore, targeting decreases in lactate levels in patients with non-hypoperfusion-related hyperlactatemia could lead to detrimental over-resuscitation. Multimodal perfusion monitoring, including capillary refill time (CRT), could aid in identifying a non-hypoperfusion-related hyperlactatemia, to which no further resuscitation might be required [2].

The ANDROMEDA-SHOCK trial, comparing CRT versus lactate-targeted resuscitation in early septic shock, demonstrated lower mortality, less organ dysfunction and treatment intensity in the CRT-targeted group [3, 4].

Considering that CRT is not an obligatory criterion of septic shock definition, our aim was to determine if baseline CRT in ANDROMEDA-SHOCK patients could identify distinct clinical phenotypes according to the risk of death, severity scores, organ dysfunction, and treatment intensity.

We performed a post hoc analysis of the ANDROMEDA-SHOCK dataset. Protocol details are published elsewhere [3]. Independently of study arm allocation, we identified patients with normal (≤3 s) or abnormal (>3 s) CRT at baseline. Univariate comparison using clinical characteristics, severity scoring, hemodynamic, perfusion variables, treatment intensity, and 28-day mortality between these two groups was performed. Results were confirmed with multivariate analysis.

ANDROMEDA-SHOCK trial recruited 424 patients, of which 25% (108) had normal CRT at baseline. Clinical characteristics of both groups are shown in Table 1. 28-day mortality was significantly different (27% vs 43%, $p=0.001$) (ESM Fig. 1). Multivariate analysis, which included significant clinical variables, confirmed that abnormal CRT at baseline was an independent determinant of 28-day mortality (OR 1.8; 95%CI[1.07–3.02]); $p=0.026$) (ESM Table 1). Additionally, we categorized our cohort according to CRT status and hyperlactatemia level (ESM Table 2). Interestingly, in patients with normal CRT, lactate values did not discriminate 28-day mortality. Moreover, patients with lactate >4 mmol/l had a significantly lower mortality when presenting simultaneous normal CRT.

Our results suggest that baseline CRT could define phenotypes of different risk among patients fulfilling the septic shock definition [1], where 25% of the cases presented the less severe phenotype. Although the overall 28-day mortality of the ANDROMEDA-SHOCK cohort was 39%, which is within the range of SEPSIS-3 mortality prediction, the addition of CRT status could aid to further improve risk stratification.

Recent studies have shown high variability in cardiovascular, immunological, and clinical phenotypes of sepsis

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Table 1 Clinical characteristics of patients

	CRT normal	CRT abnormal	*p* value
Number of patients	25 (108)	75 (316)	
Age (years)	65 [48–75]	66 [53–76]	0.13
Sex (female)	51 (55)	45 (143)	0.7
APACHE score	19 [13–24]	23 [18–29]	0.001
SOFA score	8 [6–10]	10 [7–12]	0.001
Charlson index	3 [0–5]	3 [1–5]	0.3
Randomization arm	CRT-T: 44.4 (48) LT: 55.6 (60)	CRT-T: 51.8 (164) LT: 48.2 (152)	0.2
Sepsis origin	Abdominal 28 (30) Pulmonary 34 (37) Urinary 21 (23) Other 17 (18)	Abdominal: 38 (119) Pulmonary: 29 (91) Urinary: 20 (64) Other: 13 (42)	0.1
MAP (mmHg)	68 [64–77]	65 [57–76]	0.015
CVP (mmHg)	8 [5–12]	9 [6–13]	0.5
Fluids administered before ICU admission (ml)	2000 [1500–2907]	2000 [1196–2747]	0.18
Fluid responsiveness positive state	42 (45)	62 (197)	0.001
Fluid administered in boluses between 0-8 h (ml)	500 [0–1100]	1000 [500–2250]	0.001
Fluid balance at 8-h (ml)	929 [260–1740]	1700 [855–2772]	0.001
Norepinephrine dose (mcg/kg/min)	0.13 [0.08–0.24]	0.25 [0.12–0.42]	0.001
Lactate (mmol/L)	3.0 [2.5–4.2]	3.8 [2.8–5.8]	0.001
CRT (sec)	2 [2, 3]	5 [4–7]	0.001
ScvO2 (%)	75 [69–81]	71 [62–78]	0.001
Delta pCO2(v-a)	7 [4–9]	7 [5–10]	0.06
SOFA at 24-hours	7 [4–10]	9 [6–12]	0.001
Renal replacement therapy	10 (11)	19 (61)	0.013
Mechanical ventilation	62 (67)	80 (255)	0.001
ICU length of stay (days)	5 [3–12]	6 [1–8]	0.26
28-day mortality	27 (29)	43 (137)	0.001

Baseline characteristics and clinical outcomes of septic shock patients with normal versus abnormal capillary reill time at protocol inclusion. Data at 8 and 24 h are reported for clariication purposes

Data are presented as median [IQR 25–75] or percentage (count)

CRT capillary refill time, *APACHE II* acute physiology and chronic health evaluation II, *SOFA* sequential organ failure assessment score, *CRT-T* CRT-target, *LT* lactate-target, *ICU* intensive care unit, *MAP* mean arterial pressure, *CVP* central venous pressure, *CRT* capillary refill time, *ScvO2* central venous oxygen saturation, *Delta pCO2(v-a)* difference between central venous carbon dioxide pressure and arterial carbon dioxide pressure

[5]. A simple and universally available test, like CRT, further identifies two populations of widely different risk. Implementing "one size fits all" therapies, could expose less sick patients to the burden of over-resuscitation.

These findings could also have an important impact on the triage of patients in resource-constrained settings, and future designs of septic shock clinical trials. Since this study is a post hoc analysis, results should be considered as hypothesis-generating and confirmed by future prospective studies.

This post hoc analysis of ANDROMEDA-SHOCK concludes that septic shock patients with normal CRT after initial resuscitation represent a less severe clinical phenotype, with less organ dysfunction and higher survival rates.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-020-05960-4) contains supplementary material, which is available to authorized users.

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The authors declare no conflict of interest.

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References

1. Singer M, Deustchman C, Warren Seymour C, Shankar-Hari M, Annane D, Bauer M et al (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315:801–810
2. Alegría L, Vera M, Dreyse J et al (2017) A hypoperfusion context may aid to interpret hyperlactatemia in sepsis-3 septic shock patients: a proof-of-concept study. Ann Intensive Care 7:29
3. Hernandez G, Ospina-Tascon G, Petri Damiani L et al (2019) Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock. The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA 321:654–664
4. Zampieri FG, Damiani LP, Bakker J et al (2019) Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: a bayesian reanalysis of the ANDROMEDA-SHOCK trial. Am J Respir Crit Care Med. https://doi.org/10.1164/rccm.201905-0968oc
5. Seymour CW, Kennedy JN, Wang S et al (2019) Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. JAMA 321:2003–2017

Interpretation or misinterpretation of clinical trials on septic shock: about the ANDROMEDA-SHOCK trial

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In the ANDROMEDA study, Hernandez and colleagues evaluated whether a resuscitation strategy targeting the capillary refill time (CRT) normalization (CRT strategy) could be more effective to decrease 28-day mortality than a resuscitation strategy aiming at normalizing or decreasing lactate levels by 20% every 2 h (lactate strategy), in the first 8 h of septic shock (1). Resuscitation protocol was standardized in three successive steps: if the goal was not reached at the end of a step, the investigator had to go forward to the next step until the goal was reached. On the first step, the investigators had to test fluid responsiveness. The second step was a vasopressor test in order to increase mean arterial pressure (MAP) from 65 to 80–85 mmHg. The third step consisted in an inodilator test (low dose of dobutamine or milrinone, depending on the center). The authors made the hypothesis that the CRT strategy would decrease the mortality rate by 15% (from 45% to 30%) compared to the lactate strategy.

However, they observed a reduction of 8.5% in 28-day mortality in the CRT group, that did not reach "statistical significance" [hazard ratio, 0.75 (95% CI, 0.55 to 1.02); P=.06; risk difference, –8.5% (95% CI, –18.2% to 1.2%)]. However, at day 3, the CRT strategy group had significantly less organ dysfunctions, assessed with Sepsis-related Organ failure Assessment (SOFA score) (2) [mean SOFA score, 5.6 (SD, 4.3) *vs.* 6.6 (SD, 4.7); mean difference, –1.00 (95% CI, –1.97 to –0.02); P=0.045] suggesting a beneficial effect of the CRT strategy on organ dysfunction.

Despite the fact that the main outcome did not reach the statistical significance, clinician could consider that a reduction of 20% of the relative risk of mortality is clinically relevant. Furthermore, many reasons require us to be careful with interpretation of P values and confidence intervals (3,4). Indeed, all experimental and clinical studies are considered "positive" or "negative" according to an arbitrary p value cut-off of 0.05. One should remind that this only means that the study is considered as positive if the observed statistical difference between groups is less than 5% due to hazard. However, P value is today seriously challenged (5). In 2016, the American Statistician Association (ASA) made a statement on P values, the third statement was that "*scientific conclusions decisions should not be based only whether a p-value passes a specific threshold*" (6). In 2019, the same authors published an editorial entitled "*Moving to a World Beyond P<0.05*" where they provide advice to use alternatives statistical methods to synthesize evidence across studies (i.e., meta-analysis, evidence reviews and Bayesian methods) (7). Other large trials, "negative on P value", have also been subject to Bayesian approach (8). Hence, if a strict p-value cut-off aims to assess rigorously clinical trials with statistical significance, it is also the best way to misinterpret trials data. For all these reasons, the authors of this study

decided to test different analytic methods including post-hoc Bayesian and mixed logistic regression approaches to help the interpretation of the study (9).

Bayesian approach consists on a posteriori evaluation of the credibility of an event knowing new data (4). It is a mathematical way to reallocate credibility of an event or for some data to be explained.

The primary endpoint of the new analysis was 28-day mortality, and secondary endpoints were 90-day mortality and changes in SOFA score between groups at different time points (8, 24, 48 and 72 h). The analysis has been performed using different degrees of skepticism concerning the efficacy of the CRT-based resuscitation strategy (optimistic, neutral, null or pessimistic). The authors built a Bayesian hierarchical Bernoulli regression model for the primary endpoint adjusted for 6 variables: Acute Physiology And Chronic Health Evaluation 2 (APACHE2) score (10), admission SOFA score, baseline lactate level, baseline CRT, source of infection and admission center).

Concerning the primary endpoint (28-day mortality), they observed a beneficial effect of the strategy based on CRT normalization, compared to the strategy based on lactate clearance for all hypothesis but the pessimistic one [OR =0.62 (0.38–0.92) for the null hypothesis, OR =0.63 (0.41–0.9) for the optimistic hypothesis, OR =0.67 (0.43–0.96) for the neutral, OR =0.76 (0.5–1.09) for the pessimistic one, respectively]. When looking at the 90-day mortality, no beneficial effect of resuscitation based on CRT normalization was observed in all hypothesis. Patients treated in the CRT based resuscitation group had a higher probability to have a SOFA between 0–7 at 48 and 72 h [OR =1.55 (1.02–2.37) and OR =1.52 (1.00–2.24), respectively] compared to the lactate strategy group. However, the potential beneficial effect on organ dysfunction in the CRT strategy group is possibly due to the fact that patients in the lactate strategy had a higher MAP at 72 h (85±13 *vs.* 80±12 mmHg, P<0.01) possibly requiring higher doses of norepinephrine [0.10 (0.06–0.21) *vs.* 0.1 (0.03–0.18) mcg/K/min, P<0.01] which may have artificially increased the SOFA score.

Despite some limitations that can be avoided by standardizing the measurement method of CRT (11,12) a resuscitation based on CRT target is seducing and present many advantages (e.g., non-invasive, easily performed at the bedside, a rapid recovery with patient's improvement and is available even in resource limited-setting). Therefore, the authors have concluded from this Bayesian analysis of ANDROMEDA study that "*Peripheral perfusion-targeted resuscitation may result in lower mortality and faster resolution of organ dysfunction when compared to a lactated-targeted resuscitation strategy*". However, they could also have concluded that a resuscitation protocol based on lactate clearance may result in higher mortality.

The strategy based on lactate decrease emerges from the surviving sepsis campaign's recommendations that suggests "*guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion*" (13). Nevertheless, the grade of this recommendation is weak, with a low quality of evidence. The goal of this strategy is to normalize or decrease lactate levels by 20% every 2 h by increasing arterial oxygen transport. To increase the arterial oxygen transport, the first line therapy is commonly intravascular volume expansion using crystalloids. This approach involves at least two wrong assumptions.

First, this strategy assumes the hypothesis that hyperlactatemia in septic shock is mainly due to tissue hypoperfusion with an imbalance between organ oxygen demand and blood oxygen supply. As recently recalled by Hernandez *et al.* there is few evidence that hyperlactatemia in septic shock is secondary to tissue hypoxia (14). Almost 15 years ago, Levy *et al.* elegantly showed by using microdialysis in the muscle of septic shock patients that hyperlactataemia was essentially due to exaggerated aerobic glycolysis through Na+/K+-ATPase stimulation (15). Indeed, patients in septic shock have increased beta adrenergic stimulation, with increased glycogenolysis, resulting in glucose metabolization into pyruvate. This large amount of pyruvate exceeds the capacity of Krebs cycle leading to lactate production (16). In ANDROMEDA study, significantly more patients in the lactate strategy group received epinephrine infusion compared to CRT strategy group [35 (16.5%) *vs.* 21 (9.9%), respectively, P<0.01]. Similarly, epinephrine increases lactate production through Na+/K+-ATPase activation (17). This could explain in part that patients who did not reach the therapeutic goal in the lactate strategy (decrease in lactate level by 20% every 2 h) could have received unnecessary therapeutics (e.g., fluid infusion, increasing vasopressor or inodilator) leading to worst outcome.

The second assumption is that septic shock is associated with volume loss and that optimizing arterial oxygen transport would improve the outcome. Gattinoni *et al.* showed almost 25 years ago that increasing cardiac index at a supra-normal level did not improve outcome among critically ill patients (18). More recently, 3 multicentric studies evaluating the effect of the early goal directed therapy have failed to show a beneficial effect of this strategy (19). In a recent post-hoc analysis of patient from ALBIOS

study, Gattinoni *et al.* observed a U shape relationship between ScVO2 and lactatemia, with two types of patients with hyperlactatemia at each extremity of the U curve: patients with high lactate level and a low ScVO2 (24–62%) (supposing a deficit in oxygen delivery) and patients with high lactate level and a high ScVO2 (82–98%) (suggesting a deficit in oxygen consumption). In this study, only one third of patient had a ScVO2 below 70%, suggesting that patients with impaired tissue oxygenation are more common in septic shock (20). Therefore, trying to optimize oxygen transport with fluid bolus in this population seems illogical and potentially harmful. We know from cohort studies that a positive fluid balance and a high central venous pressure (CVP) are associated with organ dysfunction (i.e., acute kidney injury, acute respiratory distress syndrome) and mortality (21-25). Indeed, fluid overload leads to high CVP, which is opposed to venous return. Fluid overload, by increasing more CVP than mean systemic pressure (MSP) decreases organ perfusion pressure by decreasing driving pressure gradient (MSP-CVP) (26).

Septic shock can no longer be today a single "package" that would be the same for all patients. As well as targeted therapies for onco-hematology patients, therapies in ICU should also be customized to various subgroups of septic patients. Since a few years, after the golden age of the "early-goal directed therapy", several authors and data have highlighted the interest of microcirculation. However, the goals of the resuscitation are still today subjects to debate. Instead of guiding the resuscitation on microcirculation disorders using CRT or skin mottling, some authors suggest to target microcirculation disorders (27). More than 15 years ago, De Backer *et al.* observed that the administration of acetylcholine restored microcirculation in the sublingual territory (assessed using an orthogonal polarization spectral imaging technique) (28). This observation suggests that an inappropriate vasoconstriction could participate to microcirculation disorders and could be reversed using vasodilators. This concept has been illustrated by Legrand *et al.* (27) as the "bottleneck-like vascular barrier" where an inappropriate arteriolar vasoconstriction decreases microcirculation blood flow. Legrand *et al.* make the hypothesis that using drugs targeting this inappropriate vasoconstriction could improve microcirculation perfusion and then organ dysfunction. In order to test this theory, prostacyclin analogue administration has been tested in patient with septic shock with high dose of norepinephrine and persistent peripheral circulation disorders (29). This strategy showed promising results, however, the absence of control group does not allow us to conclude on their effectiveness in this indication. This is actually tested in an ongoing multicentric randomized controlled clinical trial comparing ilomedin to placebo in patients with persistent peripheral circulation disorders (NCT03788837).

In summary, this post-hoc analysis of ANDROMEDA study suggests that CRT strategy compared to lactate strategy improves 28-day survival. To our opinion, this study highlights the fact that septic shock patient's resuscitation should not be guided by serum lactate levels but by microcirculatory endpoints such as CRT. Further studies should focus on tailored resuscitation targeting microcirculation.

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Footnote

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References

1. Hernández G, Ospina-Tascón GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs. Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA 2019;321:654.
2. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Med. Intensive Care Med 1996;22:707-10.
3. Wagenmakers EJ. A practical solution to the pervasive problems OFP values. Psychon Bull Rev 2007;14:779-804.
4. Kruschke JK, Liddell TM. The Bayesian New Statistics: Hypothesis testing, estimation, meta-analysis, and power analysis from a Bayesian perspective. Psychon Bull Rev 2018;25:178-206.
5. It's time to talk about ditching statistical significance. Nature 2019;567:283.
6. Wasserstein RL, Lazar NA. The ASA Statement on p -Values: Context, Process, and Purpose. Am Stat 2016;70:129-33.
7. Wasserstein RL, Schirm AL, Lazar NA. Moving to a World Beyond "p < 0.05." Am Stat 2019;73:1-19.
8. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial. JAMA 2018;320:2251.
9. Zampieri FG, Damiani LP, Bakker J, et al. Effects of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels Among Patients with Septic Shock: A Bayesian Reanalysis of the ANDROMEDA-SHOCK Trial. Am J Respir Crit Care Med 2020;201:423-9.
10. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
11. Brabrand M, Hosbond S, Folkestad L. Capillary refill time: a study of interobserver reliability among nurses and nurse assistants. Eur J Emerg Med 2011;18:46-9.
12. Kawaguchi R, Nakada T, Oshima T, et al. Optimal pressing strength and time for capillary refilling time. Crit Care 2019;23:4.
13. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43:304-77.
14. Hernandez G, Bellomo R, Bakker J. The ten pitfalls of lactate clearance in sepsis. Intensive Care Med 2019;45:82-5.
15. Levy B, Gibot S, Franck P, et al. Relation between muscle Na+ K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. Lancet 2005;365:871-5.
16. Garcia-Alvarez M, Marik P, Bellomo R. Stress hyperlactataemia: present understanding and controversy. Lancet Diabetes Endocrinol 2014;2:339-47.
17. Levy B. Lactate and shock state: the metabolic view. Curr Opin Crit Care 2006;12:315-21.
18. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. N Engl J Med 1995;333:1025-32.
19. Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med 2015;41:1549-60.
20. Gattinoni L, Vasques F, Camporota L, et al. Understanding Lactatemia in Human Sepsis. Potential Impact for Early Management. Am J Respir Crit Care Med 2019;200:582-9.
21. Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39:259-65.
22. Legrand M, Dupuis C, Simon C, et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. Crit care 2013;17:R278.
23. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care 2015;19:251.
24. Tigabu BM, Davari M, Kebriaeezadeh A, et al. Fluid volume, fluid balance and patient outcome in severe sepsis and septic shock: A systematic review. Journal of Critical Care 2018;48:153-9.
25. Montomoli J, Donati A, Ince C. Acute Kidney Injury and Fluid Resuscitation in Septic Patients: Are We Protecting the Kidney? Nephron 2019;143:170-3.
26. Legrand M, Soussi S, Depret F. Cardiac output and CVP monitoring… to guide fluid removal. Crit Care 2018;22:89.
27. Legrand M, De Backer D, Dépret F, et al. Recruiting the microcirculation in septic shock. Ann Intensive Care 2019;9:102.
28. De Backer D, Creteur J, Preiser JC, et al. Microvascular Blood Flow Is Altered in Patients with Sepsis. Am J Respir Crit Care Med 2002;166:98-104.
29. Dépret F, Sitbon A, Soussi S, et al. Intravenous iloprost to recruit the microcirculation in septic shock patients? Intensive Care Med 2018;44:121-2.

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When data interpretation should not rely on the magnitude of P values: the example of ANDROMEDA SHOCK trial

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Adequate treatment of patients with septic shock (SS) entails a reliable method to assess the circulatory requirements. A number of different indices have been tested to delineate the hemodynamic profile and to drive the treatment in patients with shock states. However, it is still an unresolved topic. Lactates represents one of the milestone to monitor the perfusion profile and drive hemodynamic resuscitation of patients in SS. High lactates, although are not a direct measure of tissue perfusion, are mainly considered a marker of tissue dysoxia shown to be associated with worst outcome in patients with sepsis and SS (1). However, although the "dysoxia/tissue hypoperfusion/anaerobic glycolysis" is the most commonly interpreted theory for lactates rise in SS, there are several other mechanisms leading to lactates hyper-production and accumulation. These mechanisms include the alteration of Na+/K+-ATPase activity enhanced by adrenergic stimuli (2), accelerated aerobic glycolysis induced by sepsis-associated inflammation, and the pyruvate accumulation due to mitochondrial pyruvate dehydrogenase reduction activity (3). Additionally, lactates kinetics could be influenced by many different factors (i.e., decreased production, dilution, oxidation, organ utilization as bioenergetic fuel) (4).

The skin is an accessible organ, mirroring the peripheral tissue perfusion through clinical non-invasive bedside parameters, such as the skin temperatures gradient, capillary refill time (CRT, which is the measure of the time necessary for the skin to return to baseline color after applying a pressure on a soft tissue), and the extent of mottling. The underlying pathophysiology mechanisms inducing skin perfusion modification are not completely understood but seems to be driven by sympathetic neuroactivation inducing local vasoconstriction (5), local endothelial dysfunction (6), leukocyte adhesion and platelet activation (7). Hernandez *et al.* in the ANDROMEDA–SHOCK trial (8) compared CRT to lactate monitor peripheral perfusion for driving the resuscitation treatment in SS patients. Prolonged CRT was already shown to be associated with organ failure and volume responsiveness in patients with circulatory failure (9), as well as to be a predictive factor of 14-days mortality in SS patients after resuscitation (10). The authors showed that a peripheral perfusion-guided resuscitation strategy was associated with lower 28-day mortality when compared to lactate-guided resuscitation strategy (35% *vs.* 43%) in SS patients, even if the difference did not reach the statistical significance (P=0.06) based on the conventional P values threshold. Thus, Hernandez *et al.* concluded that the null hypothesis of their study (absence of difference between peripheral perfusion and lactate-targeted strategies) could not be rejected. Recently, Zampieri *et al.* (11) reported

a Bayesian reanalysis of this trial (8) demonstrating that peripheral perfusion-targeted resuscitation may result in lower mortality when compared to a lactated-targeted resuscitation strategy. We agree with the authors that this 8.5% absolute risk difference in the 28-day mortality observed in the ANDROMEDA-SHOCK trial remains clinically significant despite not yet statistically significant (11). Hernandez *et al.* stating that "*among patients with SS, a resuscitation strategy targeting normalization of CRT, compared with a strategy targeting serum lactate levels, did not reduce all-cause 28-day mortality*", could be misleading for the readers who are at risk of labeling a study which such results as "negative". Indeed, interpretation of clinical trials can be challenging when dichotomous rules for rejection of the null hypothesis are applied, especially when the P value is close to the arbitrary cutoff. Data analysts too often resort to binary decisions (e.g., whether to reject or accept the null hypothesis) in settings like the ANDROMEDA-SHOCK trial (8), where this may be misleading because the clinical relevance and the physiological plausibility overcome the statistical uncertainty. The question of interest in the testing framework concerns the relative likelihood of the null and alternative hypotheses given the experimental data, but P values are heavily dependent on sample size and even a large effect may not be found in a relatively small sample size. This is the reason because an effect can be relevant even if results are still not significant. In this context, a strict binary view of statistical inference is not useful and may promote the loss of important findings that do not claim the expected level of significance while provide fundamental insight shock pathophysiology. The Bayesian approach may be helpful in contextualizing statistics because can explicitly incorporate external information when interpreting the results of a study, including biological/clinical plausibility. It is important to note as the Bayesian approach differs in many ways from the frequentist approach (12,13): (I) starting with a prior opinion about probability distribution, and then using the posterior probability distribution on the basis of both the data and the prior distribution; (II) prior information is formally incorporated in the design; (III) parameters of interest are unknown random variables; (IV) population parameters are a distribution of values reflecting uncertainty; (V) large sample size are not required; (VI) a 95% credible interval represents the 95% probability that the true value of the unknown parameter is within the limits of the interval; (VII) the P value is defined as the probability of the (null) hypothesis.

Interestingly, Zampieri *et al.* performed their study by using the R statistical computing environment (14). R, a free and open-source implementation of the S language, has become the lingua franca of the statistical computing (15), Zampieri *et al.* have made available the full R code used for their Bayesian reanalysis, making an important contribution to reproducible research (16).

Circulatory shock is a pathological situation associated with inadequate oxygen utilization by the cells and evidence of both clinical and biochemical tissue hypoperfusion. Currently available variables for the assessment of peripheral hypo-perfusion rely merely on macro-hemodynamics and established non-specific, clinical-biochemical signs. The evaluation of peripheral perfusion and its response to therapy with reliable and widely adoptable parameters has a potential to represent a more sensitive diagnostic and monitoring tool for the comprehensive assessment of cardio-vascular coupling at the bedside of patients in shock states (17). Arterial lactate may be due to the downstream consequences of yet established hypoperfusion with ongoing mitochondrial damage and the shift to anaerobic metabolism, whereas CRT allows a direct and pre-emptive evaluation of the adequacy of peripheral perfusion and its application in the perfusion-targeted resuscitation.

Bayesian analyses as either a primary or a complementary analysis should be considered to contextualized and improve clinical messages of adequately powered RCTs. In the specific case (11), it allowed to demonstrate that CRT driven treatment group was associated with lower mortality and faster resolution of organ dysfunction.

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Footnote

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References

1. Casserly B, Phillips GS, Schorr C, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Crit Care Med 2015;43:567-73.
2. Levy B, Gibot S, Franck P, et al. Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. Lancet 2005;365:871-75.
3. Alamdari N, Constantin-Teodosiu D, et al. Temporal changes in the involvement of pyruvate dehydrogenase complex in muscle lactate accumulation during lipopolysaccharide infusion in rats. J Physiol 2008;586:1767-75.
4. Garcia-Alvarez M, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. Crit Care 2014;18:503.
5. Lima A, Bakker J. Noninvasive monitoring of peripheral perfusion. Intensive Care Med 2005;31:1316-26.
6. Bourcier S, Joffre J, Dubee V, et al. Marked regional endothelial dysfunction in mottled skin area in patients with severe infections. Crit Care 2017;21:155.
7. Ait-Oufella H, Maury E, Lehoux S, et al. The endothelium: physiological functions and role in microcirculatory failure during severe sepsis. Intensive Care Med 2010;36:1286-98.
8. Hernandez G, Ospina-Tascon GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA 2019;321:654-64.
9. Jacquet-Lagreze M, Bouhamri N, et al. Capillary refill time variation induced by passive leg raising predicts capillary refill time response to volume expansion. Crit Care 2019;23:281.
10. Ait-Oufella H, Bige N, Boelle PY, et al. Capillary refill time exploration during septic shock. Intensive Care Med 2014;40:958-64.
11. Zampieri FG, Damiani LP, Bakker J, et al. Effects of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels Among Patients with Septic Shock: A Bayesian Reanalysis of the ANDROMEDA-SHOCK Trial. Am J Respir Crit Care Med 2020;201:423-9.
12. Skrepnek GH. The contrast and convergence of Bayesian and frequentist statistical approaches in pharmacoeconomic analysis. Pharmacoeconomics 2007;25:649-64.
13. van de Schoot R, Kaplan D, Denissen J, et al. A gentle introduction to bayesian analysis: applications to developmental research. Child Dev 2014;85:842-60.
14. R Core Team. R: A language and environment for statistical computing. 2019-R Foundation for Statistical Computing, Vienna, Austria. Available online: at https://www.R-project.org/
15. Mizumoto A, Plonsky L. R as a lingua franca: Advantages of using R for quantitative research in applied linguistics. Appl Linguist 2016;37:284-91.
16. Santori G. Research papers: Journals should drive data reproducibility. Nature 2016;535:355.
17. Corradi F, Via G, Tavazzi G. What's new in ultrasound-based assessment of organ perfusion in the critically ill: expanding the bedside clinical monitoring window for hypoperfusion in shock. Intensive Care Med 2020;46:775-9.

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