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REVIEW ARTICLE

Association between peripheral perfusion, microcirculation and mortality in sepsis: a systematic review

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Review

Abstract Although increasing evidence supports the monitoring of peripheral perfusion in septic patients, no systematic review has been undertaken to explore the strength of association between poor perfusion assessed in microcirculation of peripheral tissues and mortality. A search of the most important databases was carried out to find articles published until February 2018 that met the criteria of this study using different keywords: sepsis, mortality, prognosis, microcirculation and peripheral perfusion. The inclusion criteria were studies that assessed association between peripheral perfusion/microcirculation and mortality in sepsis. The exclusion criteria adopted were: review articles, animal/pre-clinical studies, meta-analyzes, abstracts, annals of congress, editorials, letters, case-reports, duplicate and articles that did not present abstracts and/or had no text. In the 26 articles were chosen in which 2465 patients with sepsis were evaluated using at least one recognized method for monitoring peripheral perfusion. The review demonstrated a heterogeneous critically ill group with a mortality-rate between 3% and 71% (median = 37% [28%–43%]). The most commonly used methods for measurement were Near-Infrared Spectroscopy (NIRS) (7 articles) and Sidestream Dark-Field (SDF) imaging (5 articles). The vascular bed most studied was the sublingual/buccal microcirculation (8 articles), followed by fingertip (4 articles). The majority of the studies (23 articles) demonstrated a clear relationship between poor peripheral perfusion and mortality. In conclusion, the diagnosis of hypoperfusion/microcirculatory abnormalities in peripheral non-vital organs was

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associated with increased mortality. However, additional studies must be undertaken to verify if this association can be considered a marker of the gravity or a trigger factor for organ failure in sepsis.

PALAVRAS-CHAVE
Perfusão;
Microcirculação;
Mortalidade;
Sepse;
Revisão

Associação entre perfusão periférica, microcirculação e mortalidade em sepse: uma revisão sistemática

Resumo Embora evidências crescentes apoiem a monitorização da perfusão periférica em pacientes sépticos, nenhuma revisão sistemática foi feita para explorar a força da associação entre a má perfusão avaliada na microcirculação dos tecidos periféricos e a mortalidade. Uma busca nas bases de dados mais importantes foi feita para encontrar artigos publicados até fevereiro de 2018 que correspondessem aos critérios deste estudo, com diferentes palavras-chave: sepse, mortalidade, prognóstico, microcirculação e perfusão periférica. Os critérios de inclusão foram estudos que avaliaram a associação entre perfusão/microcirculação periférica e mortalidade em sepse. Os critérios de exclusão adotados foram os seguintes: artigos de revisão, estudos com animais/pré-clínicos, metanálises, resumos, anais de congressos, editoriais, cartas, relatos de casos, artigos duplicados e artigos que não continham resumos e/ou texto. Foram selecionados 26 artigos nos quais 2465 pacientes com sepse foram avaliados com pelo menos um método reconhecido para monitorar a perfusão periférica. A revisão demonstrou um grupo heterogêneo de pacientes gravemente enfermos com uma taxa de mortalidade entre 3% e 71% (mediana = 37% [28%–43%]). Os métodos de avaliação mais comumente usados foram a espectroscopia na região do infravermelho próximo (Near-Infrared Spectroscopy – NIRS) (7 artigos) e a análise de imagens em campo escuro (Sidestream Dark-Field – SDF) (5 artigos). O leito vascular mais avaliado foi a microcirculação sublingual/bucal (8 artigos), seguida pela ponta do dedo (4 artigos). A maioria dos estudos (23 artigos) demonstrou uma clara relação entre má perfusão periférica e mortalidade. Em conclusão, o diagnóstico de hipoperfusão/anormalidades microcirculatórias em órgãos não vitais periféricos foi associado ao aumento da mortalidade. No entanto, estudos adicionais devem ser feitos para verificar se essa associação pode ser considerada um marcador da gravidade ou um fator desencadeante da falência de órgãos na sepse.

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and is a major public health concern.[1] Predicting and identifying potential changes in early sepsis non-survivors and treating these patients differently persists as an attractive idea to improve management and outcomes.

In the microcirculation of septic patients, the heterogeneous pattern of blood flow generates tissue hypoperfusion and incapacity of the cells to extract and adequately use oxygen, which compromises aerobic cell metabolism and organ function.[2–4] Therefore, the provision of adequate perfusion of vital organs and recovery of homeostasis continue to be essential treatment goals.[1,4] Although the monitoring of macrocirculation is traditionally used to manage systemic perfusion,[1,4] several studies have shown that monitoring peripheral microcirculation, especially in non-vital organs, is able to predict survival[2,3,5] and have provided new insights into the understanding of tissue perfusion dynamics and organ failure.[6–9]

Assessment of peripheral circulation has become easier following the introduction of new non-invasive devices as well as standardized clinical scoring systems. Microcirculation can be assessed at the bedside, directly or indirectly, on the sublingual or buccal mucosal using Orthogonal Polarization Spectral imaging (OPS), Sidestream Dark Field imaging (SDF), or Laser Doppler Flowmetry (LDF); on the muscle using Near-Infrared Spectroscopy (NIRS); on the retinal vessels using retinal Fluorescein Angiography (FA); and on the skin using the Perfusion Index (PI), mottling score, Capillary Refill Time (CRT), gradients of temperature, or the Oxygen Challenge Test (OCT).[9,10] Although increasing evidence from the literature supports the monitoring of peripheral perfusion in septic patients, normally using some of these methods, no systematic review has been undertaken to explore the strength of association between poor perfusion assessed in peripheral tissues and mortality in sepsis.

Therefore, this systematic review was motivated precisely with this purpose: to verify if there is clear evidence of this association before the development of a future guided therapy based on the bedside finding of peripheral perfusion.

Methods

Search strategy

It was used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement methodology.

The electronic search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, SCOPUS and Web of Science data bases until February 2018, to identify relevant studies. In the search strategy, filters were not used that limited the date of publication, language and type of the article. A time limit for the initial search date was not used. Although it seems to hamper research by increasing time, the goal was precisely to make the search as broad as possible. The study designs were not restricted because although ''mortality risk assessments'' are classically studied in ''observational studies'' (prospective or retrospective). However, this selection was made in manual screening by each of the authors. The structured search strategy was designed to identify any published document assessing the peripheral perfusion (using any method) and mortality in patients with sepsis, or any information regarding these words, in order to make the review as comprehensive as possible.

The search strategy included keywords and medical subject headings for sepsis, microcirculation, mortality and peripheral perfusion.

Outcomes

The primary outcome was to assess the association between poor perfusion in peripheral tissues and mortality in sepsis.

Initially, the titles related to the topic were screened. This selection was based on the titles that addressed as main idea the peripheral perfusion index and mortality in patients with sepsis. At the end of this step, any duplicate titles were excluded.

The articles identified by the initial search strategy were jointly evaluated by two authors. In the cases of non-consensus, an independent review was obtained. The articles were selected according to the inclusion criteria, namely: studies that evaluated the correlation between the peripheral perfusion index and mortality in patients with sepsis. Review articles, animal studies, pre-clinical studies, meta-analyses, abstracts, annals of congress, editorials, letters, case reports, duplicate studies and articles that did not present abstracts and/or had no text wer e excluded.

Subsequently, two authors jointly reviewed the abstracts of the selected articles to confirm that they were relevant to the study. When the title and the abstract did not provide enough information, the article was read in its entirety, thus preventing important studies from being left out of this systematic review.

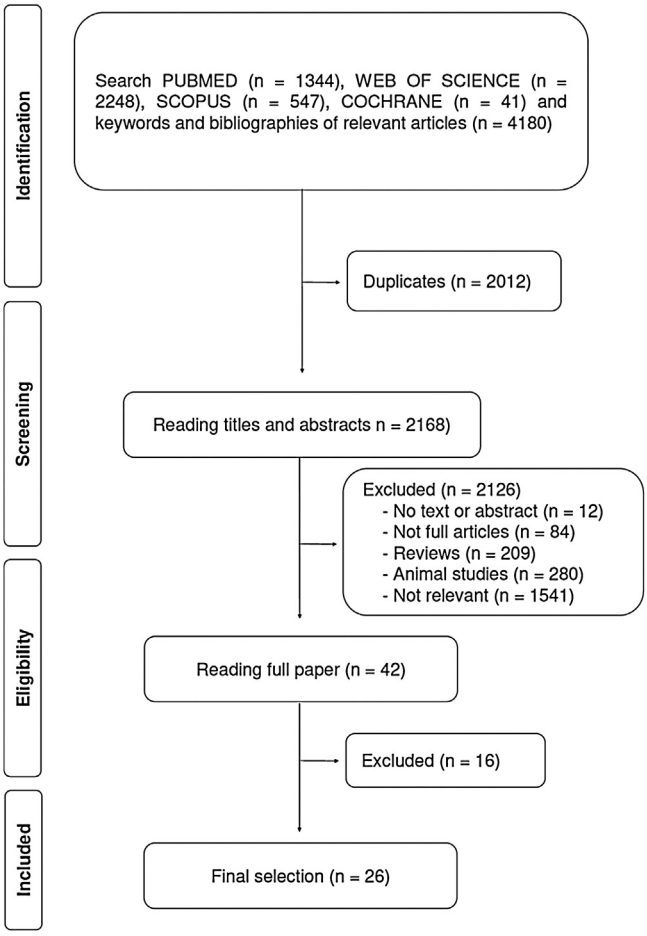

Figure 1 Flowchart of included articles. The articles that was not related to primary studies of prognosis were excluded according to the following exclusion criteria: duplicated studies, articles did not present abstracts and/or no text, articles not shown in full (abstracts, conference reports, conference posters, editorials, letters, case reports), reviews or meta-analyses, animal or pre-clinical studies, and whose subject did not meet the criteria of this study.

Data extraction

The data were extracted by one reviewer and checked by another. The following information was extracted from all studies: first author, year of publication and country, methodology, results, source of sepsis and indexes related to severity, such as the Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores, Mean Arterial Pressure (MAP) and Heart Rate (HR), peripheral perfusion, oxygen saturation, and sepsis mortality. The search strategy is shown in Fig. 1 .

Quality assessment

To estimate the quality of included studies, the original version (for case-control and cohort studies) and a modified version (for cross-sectional studies) of the Newcastle-Ottawa Scale (NOS) were used. The analyzes were carried out by two researchers independently. The NOS criteria were scored based on three aspects: (i) selection, (ii) comparability and (iii) exposure or outcome. Total NOS scores range from 0 (lowest) to 9 (highest) for case-control and cohort studies, and 0 to 10 for cross-sectional studies. Those who had a score above the median were classified as high quality studies: five for case-control and cohort studies and six for cross-sectional studies. Any discrepancy between the two investigators on the NOS scores of enrolled studies was resolved by discussion or consultation with a third investigator.

Results

Selection of studies

We found 1344 articles in PubMed, 2248 in Web of Science, 547 in Scopus and 41 in Cochrane, giving a total of 4180 articles. After excluding 2012 duplicate articles, we proceeded to read 2168 titles and abstracts. After discarding 12 articles that did not present abstracts and/or no text. We also excluded 84 articles not shown in full (abstracts, conference reports, conference posters, editorials, letters, case reports), 209 articles were also excluded for not present reviews or meta-analyses, in animals or preclinical studies 280 were excluded, and whose subject did not meet the criteria of this study excluded 1541 articles. 42 articles were selected for a complete reading. After this step, 26 articles were finally selected (Fig. 1). There was a high level of agreement on inclusion/exclusion between the two researchers who examined the articles found in the search.

The main methods for monitoring peripheral perfusion that were found in the reviewed studies are summarized in Table 1.

The patients studied were heterogeneous and critically ill, which is typical of sepsis (Table 2). The studies included a total of 2465 patients. The APACHE scores ranged from 4 to 28.8 (median = 19.5 [15.7–21.5]) for sepsis patients, and from 18 to 23 (median = 21 [20–23]) for severe sepsis patients, while SOFA scores ranged from 4 to 13 (median = 10 [8–11]) for the group of patients with sepsis and 4 to 11 (median = 8.3 [6–9.5]) for the severe sepsis group. MAP ranged from 67 to 89 mmHg (mean = 76.77 ± 5.94 mmHg) for the sepsis patients and from 69 to 75 mmHg (mean = 71 ± 2.28 mmHg) for severe sepsis patients. HR for the sepsis patients ranged from 88 to 115 bpm (mean = 102.9 ± 7.35 bpm) and for the severe sepsis patients of 92 to 114 bpm (mean = 103.2 ± 7.8 bpm) (Table 2).

Regarding the quality of the studies, 77% of the case-control, 66% of the cohort and 64% of the cross-sectional studies were considered of high quality, according to the criteria used by the authors.

Association between peripheral perfusion, microcirculation and mortality in sepsis

The methods for vascular perfusion measurement most used were Near Infrared Spectroscopy (NIRS) (7 articles) and Sidestream Dark Field (SDF) imaging (5 articles). The microvascular bed most studied was the sublingual/buccal microcirculation (8 articles), followed by finger circulation (4 articles) (Table 3).

Data on microvascular perfusion and mortality in 23 of the articles included in the study (Table 3) clearly showed an association between poor peripheral perfusion and high mortality, with only 3 showing no association.

Thus, of the 26 articles included in the review, 5 evaluated patients in emergency departments and 21 evaluated patients in Intensive Care Units (ICU) (Table 3). Mortality ranged from 3% to 71% (median = 37% [28.6–43.7]).

Studies have related the time of evaluation of the microcirculation or peripheral perfusion (Table 4). As can be observed, this varied between the first few hours during fluid resuscitation up to five days after admission and/or inclusion of patients in studies. Also, one study monitored peripheral perfusion 3–6 months after inclusion. However, these measurements were not included in the prediction of mortality.

Discussion

Although the study of perfusion/flow disturbances in critically ill patients belongs to a growing area of research, to the best of our knowledge this is the first study to systematically review and evidence the association between the bedside diagnosis of impaired perfusion in peripheral tissues and higher mortality in human sepsis. The main strength of this study is the application of a robust systematic review of a large total number of patients, with varying degrees of sepsis severity and including studies from high, middle and low-income countries. This last point deserves special consideration because sepsis etiology, clinical evolution, demographic factors and management resources are different in different countries[35] leading to heterogeneity in clinical characteristics and variable outcomes.[35] Another strength was the presence of studies performed in both emergency departments and intensive care units, meaning that the results of the review are probably not dependent on the management environment. In this large sample, 23 of 26 articles consistently showed a statistically significant association between poor peripheral perfusion and high mortality in sepsis. The evidence that the prognostic association remained consistent in these 23 articles, despite such a heterogeneous sample, suggests an important value of this review to generalize the results. In addition, although the three remaining articles found no similar association, the small number of patients in these studies limits conclusions about a possible relationship between variables.

In spite of the advances in critical care, sepsis and septic shock are still major causes of morbidity and mortality.[1] The macrocirculation monitoring and recovery of vital function remain as the cornerstones of sepsis management.[1,4] However, the monitoring of the perfusion

Table 1 Main methods used to directly or indirectly monitor peripheral perfusion in sepsis studies with mortality predictions.

Methods	How to interpret the measurement/estimation of peripheral perfusion[9,10,31]
Orthogonal Polarization Spectral imaging (OPS) and Sidestream Dark Field imaging (SDF)	Techniques that use reflected light to produce real-time images of microcirculation. Using a hand-held video-microscope, OPS and SDF can assess microvascular density and perfusion. A semi-quantitative score (Microcirculatory Flow Index – MFI) is usually used to characterize microcirculatory flow. Microcirculatory density can be assessed as the Total Vessel Density (TVD) and Perfused Vessel Density (PVD). The PVD/TVD ratio is used to express the Proportion of Perfused Vessels (PPV). Quantitative assessment of microcirculation can also be performed.
Near Infrared Spectroscopy (NIRS)	A technique that uses the principles of light transmission/absorption to measure tissue oxygen saturation (StO_2) and other parameters such as concentration of myoglobin and oxidized cytochrome. It provides a global assessment of oxygenation in all microvascular compartments (arterial, venous, and capillary). StO_2 is partly related to blood flow and has been shown to be a parameter for determining the balance between oxygen supply and oxygen demand. Blood flow can also be estimated using venous occlusion and hemoglobin concentration. Conversely, arterial occlusion can be used to study microvascular reactivity.
Transcutaneous oxygen measurement and the Oxygen Challenge Test (OCT)	Subcutaneous partial oxygen pressure ($PtcO_2$) can be measured using non-invasive transcutaneous probes. The Oxygen Challenge Test (OCT) consists of the $PtcO_2$ response to increasing the fraction of inspired oxygen (Fio2) to 100% for a 5–15 minutes period. It is related to global oxygen delivery and tissue perfusion. Therefore, the $PtcO_2$ increases with increasing FiO2 in normal perfusion states, whereas $PtcO_2$ poorly responds to increasing FiO_2 in hypoperfusion states.
Temperature values and gradients	Skin temperature is a traditional sign of peripheral vasoconstriction and reduced blood flow; cold skin temperature is related to a lower cardiac index and higher arterial lactate. Temperature gradients can better reflect cutaneous blood flow than skin temperature itself.
Skin mottling	Defined as ''patchy skin discoloration'', it usually manifests around the knees and might extend to other sites such as the fingers and ears. It is a result of the heterogeneous vasoconstriction of small vessels and is an easily assessed sign of peripheral hypoperfusion. Skin mottling scores range from 0 to 5 based on the extension from the knees to the peripheral areas.
Oximetry-derived Perfusion Index (PI)	Represents the ratio between the pulsatile and nonpulsatile component of photoplethysmography signal from oximetry. As blood flow changes affect only the pulsatile (arterial) component of the signal, PI is considered a numerical non-invasive measure of peripheral perfusion.
Capillary Refill Time (CRT)	Defined as ''the time needed for skin color to return to baseline on a fingertip after application of blanching pressure'', thus estimating the peripheral capillary blood flow

Table 1 (*Continued*)

Methods	How to interpret the measurement/estimation of peripheral perfusion[9,10,31]
Laser Doppler Flowmetry combined with Visible Light Spectroscopy (LDF/VLS)	LDF provides continuous measurement of microcirculatory blood flow in arbitrary perfusion units using the principle of doppler shift: the frequency change that light undergoes when reflected by moving objects, e.g. red blood cells.
VLS is performed by emitting light in the visible range (white light) and detecting the back scattered light. The main absorber, haemoglobin, changes its absorption characteristics with oxygenation (HbO2).	
Retinal fluorescein angiography	Fluorescein is given intravenously and retina images are obtained using a digital camera. The Retinal Arterial Filling Time (RAFT) is used to measure microvascular flow.

of peripheral non-vital organs or tissues such as the sublingual mucosa, muscles and the skin has received increasing interest in relation to improved management.[9,10] In addition to the safety and non-invasiveness of these methods,[10] robust evidence has shown that impaired perfusion in these organs or tissues are associated with worse organ failure in the subsequent 24 hours.[12] Furthermore, perfusion in non-vital organs or tissues deteriorates earlier, presents markedly different normalization rates[7] and persists even after correction of systemic macro-circulation parameters.[2] This peculiar phenomenon is known in the literature as the ''dissociation between macro and microcirculation''[36] or ''loss of hemodynamic coherence''.[13] Among the pathophysiology signals of this phenomenon are nitrosative/oxidative injuries, endothelial dysfunction and vasomotor dysregulation.[13,37]

Several experimental reports, *in vivo* and *in vitro*, showed that microcirculation disturbances and hypoperfusion in sepsis affected all studied sites including vital and non vital organs as the skin, muscle, eye, tongue, gut, liver, heart and even the brain.[37] Hence, these disturbances seem to be ubiquitous. Thus, at least theoretically, it was possible to include several methods for assessing several tissues, in the same review. In fact, our search strategy found articles using methods of evaluation of several different and easily accessible tissues at bedside (skin, muscle, sublingual mucosa and retina) with findings that are clearly consistent with the pre-clinical evidences previously cited.

However, although the association between impaired perfusion in peripheral tissues and higher mortality in sepsis seems clear, some concerns should be pointed out. The main question of this review was to verify if peripheral hypoperfusion, diagnosed at bedside using any recognized method, is related to mortality. Although this predictive finding has been confirmed by several methods and is related to the same ''clinical meaning'', these results still can not be considered interchangeable. Firstly, the methods used in the studies for perfusion assessment have clear operational differences (Table 1). These technical differences could imply different patients with aptitude for examination and, therefore, it is not possible to rule out a selection bias between methods. Secondly, the microvascular homeostasis of different organs or tissues such as the skin, muscles, the retina and the sublingual mucosa are mediated by different vasoactive mediators,[38–40] which do not have the same degree of impairment or the same pathogenic role in sepsis.[41,42] Moreover, sepsis causes perfusional heterogenicity with important disparities in regional tissue blood flow.[4] All these factors were evidenced in a study by Boerma et al.[43] which found a lack of correlation between simultaneously evaluated skin and sublingual microcirculatory alterations after initial resuscitation in septic patients. Therefore, it is highly plausible that impaired microcirculation in the different studied tissues may not have the same pathophysiological significance or contribute to an unfavorable prognosis despite significant similarities from a clinical point of view.

Particular consideration should be given to the NIRS method. Although NIRS is a recognized method of estimating peripheral perfusion,[9,10] it is only partly related to blood flow as it is also related to other factors involved in oxygen supply and oxygen consumption, which are also determinants of tissue oxygenation.[4,9,10] This could explain why some articles that also evaluated NIRS and mortality in septic patients were not found in the initial keyword database search but only through checking the references of the identified studies. These studies are important in the field and often cited in the literature, namely those by Marín-Corral et al.,[44] Colin et al.,[45] Vorwerk and Coats,[46] and Payen et al.[47] Although they did not fulfill the current review's inclusion criteria, it is still important to emphasize that 3 of these 4 studies also showed a clear association between lower oxygenation/perfusion and higher mortality.

Table 2 Characteristic and methodological qualities of included studies and characteristics of septic patients.

Reference (Country)	Study design	Source of Sepsis	Age Mean ± SD or Median (IQR)	APACHE II Mean ± SD or Median (IQR)	SOFA Mean ± SD or Median (IQR)	MAP Mean ± SD/SE or Median (IQR)	Heart Rate Mean ± SD or Median (IQR)	Arterial Lactate Mean ± SD or Median (IQR)	NOS Score
De Backer et al.,[11] (Belgium)	Single-center prospective study	Abdominal, Genitourinary, Respiratory, Soft tissues, Others	Healthy volunteers: 30 (26–36) years; Patients before surgery: 66 (56–74) years Acutelly ill noninfected patients: 64 (52–66) years Septic patients: 61 (50–72) years	N/A 5 (3-5) 10 (7-20) 21 (17-25)	N/A 0 (0-0) 3 (1-8) 13 (10-15)	82 (80-87) 91 (79-99) 88 (75-94) 71 (63-79)	69 (64-72) 68 (65-74) 69 (63-106) 105 (91-110)	N/A N/A 1.4 (1.3–1.7) 2.2 (1.5–3.4)	6
Sakr et al., [2] (Belgium)	Single-center prospective study	Abdominal, Genitourinary, Respiratory, Others	All Patients: 66 (51–78) Survivors: 61 (48–78) Nonsurvivors: 68 (56–78)	16 (13-19) 15 (12-17) 19 (9-14)	10 (9-12) 9 (9-11) 11 (9-14)	70 (63-79) 72 (66-80) 67 (61-76)	104 (96-118) 109 (94-121) 101 (98-117)	2.1 (1.2–3.4) 1.7 (1.2–2.4) 2.5 (1.5–4.0)	7
Doerschug et al.,[3] (United States of America)	Single-center prospective study	Data not shown	Severe sepsis patients Median - 55 Minimum - 40 Maximum - 85	Data not shown	9 2 18	69 55 90	92 72 121	3.0 1.1 10.3	6
Trzeciak et al.,[12] (United States of America)	Single-center prospective study	Abdominal, Genitourinary, Respiratory, Skin, soft tissue, Undetermined	All septic patients 61 ± 15 Survivors N/A Nonsurvivors N/A	Data not shown	5.8 ± 3.8 4.0 ± 3.2 8.3 ± 3.2	71 ± 10 N/A N/A	Data not shown	N/A 2.4 ± 1.5 5.8 ± 4.5	6
Leone et al.,[14] (France)	Single-center retrospective study	Respiratory Abdominal Genitourinary Skin, CNS	Survivors 59 (40–67) Nonsurvivors 60 (55–73)	Data not shown	Data not shown	79 (72–87) 80 (71–84)	100 (85–114) 94 (88–115)	2.3 (1.4–2.9) 2.5 (1.5–4.7)	7

Table 2 (*Continued*)

Reference (Country)	Study design	Source of Sepsis	Age Mean ± SD or Median (IQR)	APACHE II Mean ± SD or Median (IQR)	SOFA Mean ± SD or Median (IQR)	MAP Mean ± SD/SE or Median (IQR)	Heart Rate Mean ± SD or Median (IQR)	Arterial Lactate Mean ± SD or Median (IQR)	NOS Score
Spanos et al.,[15] (United Kingdom)	Single-center prospective study	Abdominal, Genitourinary, Respiratory, Neurological, Soft tissue, Others.	Sepsis 33 (25–58) Severe sepsis 66 (45–82) Survivors Nonsurvivors	8 ± 5 18 ± 7 N/A N/A	Data not shown	88 ± 15 70 ± 16 N/A N/A	115 ± 15 114 ± 25 N/A N/A	N/A N/A 1.8 (1.2-2.4) 2.7 (1.4-5.4)	6
Sakr et al.,[16] (Germany)	Single-center prospective study	Respiratory, Abdominal, Blood stream Others	All patients 61 ± 11	28.8 ± 6.4	10.6 ± 3.4	Data not shown	Data not shown	Data not shown	5
Ait-Oufella et al.,[17] (France)	Single-center prospective study	Respiratory, Abdominal, Genitourinary Soft tissue, Others	All patients 66 ± 16	Data not shown	11.5 (8.5 – 14.5)	Data not shown	Data not shown	Data not shown	5
Rodriguez et al.,[18] (Spain)	Single-center prospective study	Abdominal, Genitourinary Respiratory	All Patients 65.0 ± 12.3 Survivors 61.0 ± 14.9 Nonsurvivors 68.5 ± 9.0	24.4 ± 7.5 19.2 ± 5.1 28.1 ± 6.4	9.0 ± 2.6 7.1 ± 1.3 10.4 ± 2.5	73.6 ± 7.3 75.9 ± 7.3 71.8 ± 8.1	Data not shown	N/A 1.2 ± 0.75 2.32 ± 1.25	6
Shapiro et al.,[19] (United States of America)	Multicenter prospective study	Data not shown	Septic shock 68 ± 16 Sepsis 55 ± 17 Control 68 ± 16	Data not shown	Data not shown	75 ± 19 89 ± 16 96 ± 16	Data not shown	3.5 ± 2.5 1.7 ± 1.1 1.4 ± 0.7	7
Ait-Oufella et al.,[20] (France)	Single-center prospective study	Respiratory, Abdominal, Genitourinary Soft tissue	All patients 68 ± 15 Nonsurvivors N/A Survivors N/A	Data not shown	11 (9-15) 15 (13-19) 9 (6-10)	75 ± 14 74 ± 12 79 ± 14	Data not shown	5.4 ± 4.8 8.8 ± 5.0 2.2 ± 1.5	5
Edul et al., [21] (Argentina)	Single-center prospective study	Abdominal Respiratory Genitourinary Intravascular Bone	Survivor 69 ± 13 Nonsurvivor 72 ± 13	22 ± 5 23 ± 8	9 ± 3 11 ± 2	78 ± 13 72 ± 8	88 ± 12 103 ± 17	1.9 ± 1.1 4.1 ± 3.8	6

Table 2 (*Continued*)

Reference (Country)	Study design	Source of Sepsis	Age Mean ± SD or Median (IQR)	APACHE II Mean ± SD or Median (IQR)	SOFA Mean ± SD or Median (IQR)	MAP Mean ± SD/SE or Median (IQR)	Heart Rate Mean ± SD or Median (IQR)	Arterial Lactate Mean ± SD or Median (IQR)	NOS Score
De Backer et al.,[22] (Belgium)	Single-center retrospective study	Abdominal, Genitourinary Respiratory, Skin	All patients 69 (55–76) Survivors N/A Nonsurvivors N/A	N/A 20 (17-27) 23 (18-28)	N/A 10 (8-11) 11 (9-14)	N/A 71 (66-78) 69 (64-75)	N/A 102 (88-117) 105 (94-116)	2.1 (1.3–3.3) 1.9 (1.2–2.8) 2.4 (1.4–4.0)	7
He et al.,[5] (China)	Single-center prospective study	Abdominal, Bloodstream Genitourinary Respiratory, Soft tissue, Unknown	Survivors 58 ± 16 Nonsurvivors 67 ± 16	18 ± 6 20 ± 6	9 ± 2 10 ± 2	Data not shown	Data not shown	2.3 ± 2.0 5.6 ± 4.9	4
Hernandez et al.,[23] (Chile, Argentina, and the Netherlands)	Multicenter retrospective study	Abdominal, Catheter related Genitourinary Respiratory,	All patients 65 (18-84)	21 (18-25)	10 (7-12)	67 (61-72)	Data not shown	2.3 (1.3-4.5)	5
Ait-Oufella et al.,[24] (France)	Single-center prospective study	Abdominal, Genitourinary Respiratory, Soft tissue	All patients 69 ± 14 Nonsurvivors N/A Survivors N/A	Data not shown	10 (7-14) 13 (9-15) 8 (7-11)	76 ± 10 73 ± 10 78 ± 11	Data not shown	4.5 ± 4.6 7.7 ± 5.8 2.5 ± 1.4	8
Mari et al.,[25] (France)	Single-center prospective study	Respiratory Abdominal Soft tissue Genitourinary Others	Survivors 54 ± 19 Nonsurvivors 62 ± 12	Data not shown	9 ± 4 (T0) 8 ± 3 (T24) 11 ± 3 (T0) 11 ± 3 (T24)	80 ± 11 (T0) 82 ± 13 (T24) 79 ± 14 (T0) 78 ± 14 (T24)	100 ± 23 (T0) 96 ± 22 (T24) 105 ± 30 (T0) 96 ± 21 (T24)	2.9 ± 2.4 (T0) 1.7 ± 1.1 (T24) 3.7 ± 2.2 (T0) 3.3 ± 2.1 (T24)	5
Galbois et al.,[26] (France)	Single-center prospective study	Abdominal, Genitourinary Respiratory, Others	All patients 58.7 (52.4-68.5)	14 (12-18)	Data not shown	Data not shown	Data not shown	Data not shown	6
Rasmy et al.,[27] 2015 (Egypt)	Single-center prospective study	Abdominal Respiratory Soft tissue	All patients 50 ± 17.9 Vasopressors 54 ± 16.5 No vasopressors 45 ± 19	21 ± 11 21 ± 6 20 ± 16	4 ± 2 5 ± 2 3 ± 2	N/A 63 (55-66) 80 (69-95)	N/A 120 (102-134) 105 (100-123)	N/A 4.5 ± 3.4 1.7 ± 1.1	8

Table 2 (*Continued*)

Reference (Country)	Study design	Source of Sepsis	Age Mean ± SD or Median (IQR)	APACHE II Mean ± SD or Median (IQR)	SOFA Mean ± SD or Median (IQR)	MAP Mean ± SD/SE or Median (IQR)	Heart Rate Mean ± SD or Median (IQR)	Arterial Lactate Mean ± SD or Median (IQR)	NOS Score
Rodríguez et al.,[28] (Spain)	Single-center prospective study	Respiratory	All Patients 55.0 ± 16.3 Suvirvors 52.9 ± 17.0 Nonsurvivor 63.0 ± 14.0	15.6 ± 6.3 14.2 ± 3.9 21.0 ± 10.9	4.2 ± 1.9 3.9 ± 1.4 5.0 ± 3.4	Data not shown	Data not shown	Data not shown	5
Bourcier et al.,[29] (France)	Single-center prospective study	Respiratory Abdominal Genitourinary Soft tissue Other	Severe sepsis 65 (56-73) Septic shock 68 (60-83)	Data not shown	4 (3-5) 12 (8-14)	75 (69-84) 71 (67-76)	Data not shown	1.2 (0.9-1.9) 2.3 (1.4-6.0)	8
Houwink et al.,[30] (Netherlands)	Single-center retrospective cohort study	Data not shown	All patients 64.0 ± 14.4	0.34 (0.16–0.60) APACHE IV	7.8 ± 3.7	76.9 ± 21	Data not shown	1.9 (1.2–3.5)	4
Erikson et al.,[31] (Finland)	Single-center prospective study	Respiratory Abdominal Genitourinary Soft tissue Unknown	All patients 62.1 (50.6–75.8)	22 (18–25)	8 (5–10)	73.9 (68–88)	Data not shown	1.9 (1.3–2.5)	8
Fontana et al.,[32] (Belgium)	Single-center retrospective cohort study	Respiratory Abdominal Genitourinary Skin, others	All patients 64 ± 16; Severe sepsis 66 ± 16; Septic shock 64 ± 16	22 (17-28) 23 (17-27) 21 (17-28)	10 (8-12) 8 (6-10) 10 (9-12)	70 (67–77) 72 (66–76) 69 (66–78)	104 (92–120) 103 (91–120) 107 (94–121)	2.0 (1.3–3.2) 1.9 (1.2–3.2) 2.1 (1.5–3.3)	9
Lara et al.,[33] (Chile)	Single-center prospective study	Abdominal Respiratory Genitourinary CNS, Skin Others	All patients 67 ± 18	16 (10-21)	4 (2-7)	84 ± 20	110 ± 21	4.3 ± 2.5	8
Macdonald et al.,[34] (Australia)	Multicenter, prospective study	Respiratory Genitourinary skin Soft-tissues	Control 61 (44–75) Sepsis 68 (52–81)	Data not shown	1 (0–1) 4 (2–6)	Data no shown	108 ± 18 109 ± 23	1.8 ± 0.8 2.7 ± 2.1	6

APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; MAP, mean arterial pressure; DAA, drotrecogin alfa activated; SD, standard desviation; SE, standard error; N/A, not available; CNS, central nervous system; NOS, Newcastle-Ottawa scale for quality assessment of studies.

Table 3 Association between diagnosis of peripheral hypoperfusion and mortality in sepsis.

Reference	Methodology	Main results	
		Mortality	Peripheral perfusion *vs* mortality
De Backer et al.[11]	Adults from an ICU; Groups: Control (n = 10), patients with sepsis (n = 50), patients before cardiac surgery (n = 16) and acutely ill non-infected patients (n = 5). Sublingual microcirculation was investigated with OPS imaging.	44% (follow-up time was not clearly stated)	Proportion of perfused small vessels was reduced in septic patients when compared to the control group. The most severe impairments in microvascular blood flow were found in non-survivor septic patients.
Sakr et al.[2]	Adults from an ICU; Groups: control group (4) and septic shock (n = 46). Sublingual microcirculation was investigated with OPS imaging.	43% at 7 days	At the onset of shock, survivors and non-survivors had similar vascular densities and percentages of perfused small vessels. Small vessel perfusion improved over time in survivors but not in non-survivors. Microcirculatory alterations were similar in those who died multiple organ failure (MOF) after resolution of the shock and those who died of shock.
Doerschug et al.[3]	Adults from an ICU; Groups: Control (n = 15) and severe sepsis (n = 24). Microvascular flow was estimated by the NIRS method.	33% at 30 days	This study showed that microvascular hemoglobin was significantly reduced in septic patients. Also, the rate of tissue oxygen consumption and the rate of increase in StO_2 during reactive hyperemia were significantly slower in septic patients. Resting StO_2 measured 24 h after the onset of organ dysfunction was not associated with organ failure or survival at 7, 14, or 30 days.
Trzeciak et al.[12]	Adults from an ED and ICU; Groups: Control (n = 5) and severe sepsis/septic shock (n = 26). The sublingual microcirculation was assessed by OPS imaging.	42% (In-hospital mortality)	Early microcirculatory indices (lower flow velocity and heterogeneous perfusion) were more markedly impaired in non-survivors compared to survivors. These same indices were more markedly impaired with increasing severity of systemic cardiovascular dysfunction.
Leone et al.[14]	Adults from an ICU; Groups: No control group and septic shock (n = 42). Tissue oxygen saturation (StO_2) was monitored using the NIRS method.	31% at 28 days	The StO_2 values were significantly lower in the non-survivors than in the survivors. In septic shock patients, tissue oxygen saturation below 78% was associated with increased 28-day mortality.
Spanos et al.[15]	Adults from an ED; Groups: Control (n = 16), sepsis (n = 29) and severe sepsis (n = 19). The sublingual microcirculation was evaluated using SDF imaging.	3% sepsis 37% severe sepsis at 28 days	Microvascular flow index and perfused vessel density were small in the severe sepsis group compared to the sepsis group. The proportion of perfused vessels was significantly reduced in those patients who did not survive.
Sakr et al.[16]	Adults from ICU; Groups: healthy volunteers (n = 20), ICU control group (n = 8) and septic shock (n = 21). The perfusion was measured with LDF/VLS.	47% in-ICU mortality	Buccal mucosal HbO2 within 24 h of onset of septic shock was lower in non-survivors than in survivors. Buccal mucosal flow increased during the 2nd day of septic shock in survivors and decreased thereafter.
Ait-Oufella et al.[17]	Adults from an ICU; Groups: No control, septic shock (n = 60). The microvascular perfusion was studied using the skin motlling score.	45% at 14 days	The mottling score was a strong predictor of mortality, reaching an odds ratio of 74 when the score was 4-5.

Table 3 (*Continued*)

Reference	Methodology	Main results	
		Mortality	Peripheral perfusion *vs* mortality
Rodriguez et al.[18]	Adults from an ICU; Groups: Control (n = 50) and septic shock (n = 19). The regional oxygen saturation index (rSO_2) was obtained in the brachioradialis muscle. Measurements were performed using the NIRS method.	57 % (follow-up time was not clearly stated)	In septic shock, rSO_2 values were lower in non-survivors than in survivors at baseline, 12 hours and 24 hours after ICU admission.
Shapiro et al.[19]	Adults from an ED; Groups: control group (n = 50), septic shock (n = 58) and sepsis (n = 60). The perfusion was assessed by tissue StO_2 using the NIRS method.	Sepsis 5% septic shock 38% in-hospital mortality	NIRS measurements for the initial StO_2, StO_2 occlusion slope and StO_2 recovery slope were lower in patients with septic shock compared to septic patients. The recovery slope was most strongly associated with organ dysfunction and mortality. However, StO_2 was not different between survivors and non-survivors, with a poor area under the curve for mortality (0.56).
Ait-Oufella et al.[20]	Adults from an ICU; Groups: No control group and septic shock (n = 52). The perfusion was assessed by tissue StO_2 measured using the NIRS method around the knee.	48% at 14 days	After initial septic shock resuscitation, lower StO_2 measured around the knee is a strong predictive factor of 14-day mortality.
Edul et al.[21]	Adults from an ICU; Groups: control group (n = 25) and septic shock (n = 25). Sublingual microcirculation was evaluated using SDF imaging.	56% in-hospital mortality	Using a quantitative assessment of SDF, the non-survivors exhibited decreased perfused capillary density, proportion of perfused capillaries, and microvascular flow index along with increased heterogeneity flow index compared with the survivors.
De Backer et al.[22]	Adults from an ICU; Groups: No control group and severe sepsis (n = 252). Sublingual microcirculation was evaluated with SDF or OPS imaging.	51% in-ICU mortality	Survival rates decreased markedly with severity of alterations in the proportion of perfused small vessels (the lower quartiles). Mortality was significantly higher in patients with lower microvascular perfusion measured by these methods.
He et al.[5]	Adults from an ICU; Groups: Control (n = 20) and septic shock (n = 46). Oximetry-derived PI and 10 min-OCT were used to estimate perfusion.	43% in-ICU mortality	The PI and OCT were predictive of mortality for septic patients after resuscitation. The sensitivity and specificity for mortality were 65% and 92%, respectively, for the PI. The sensitivity and specificity were 65% and 96%, respectively, for the OCT.
Hernandez et al.[23]	Adults; Groups: No control group and septic shock (n = 122). Sublingual microcirculation was evaluated using SDF imaging.	33% in-hospital mortality	Perfused vessel density was significantly related to organ dysfunctions and mortality in septic shock patients, particularly in patients exhibiting more severe abnormalities (lowest quartile of distribution for this parameter).
Ait-Oufella et al.[24]	Adults from an ICU; Groups: No control and septic shock (n = 59). The perfusion was evaluated using CRT on the finger and on the knee area.	36% at 14 days	The CRT was strongly predictive of mortality. The area under the curve for prediction was 84% (75–94) for the finger measurement and 90% (83–98) for the knee area.

Table 3 (*Continued*)

Reference	Methodology	Main results	
		Mortality	Peripheral perfusion *vs* mortality
Mari et al.[25]	Adults from an ICU; Groups: no control group and septic shock (n = 56). Peripheral perfusion assessment was measured using 15 minutes-OCT.	31% at 28 days	At admission (T0), 15 min-OCT was similar between survivors and non-survivors. 24 h after admission (T24), survivors had a significantly higher OCT value than non-survivors.
Galbois et al.[26]	Adults from an ICU; Groups: Control (n = 75) and patients with liver cirrhosis admitted for septic shock (n = 42). Skin perfusion was assessed by the skin mottling score and tissue StO_2 measured using the NIRS method.	71% at 14 days	Mottling score and knee StO_2 at 6 h after admission were very specific predictors of 14-day mortality in patients with cirrhosis and septic shock.
Rasmy et al.[27]	Adults from an ICU; Groups: No control group and severe sepsis (n = 36), divided in treated with vasopressors (n = 21) and without vasopressors (n = 15). Oximetry-derived PI was used to measure peripheral perfusion.	40% at 28 days	PI was able to predict mortality with varying sensitivity and specificity. The best cut-off of PI was 0.21 (sensitivity 86% and specificity 90%).
Rodríguez et al.[28]	Adults from an ICU; Groups: No control group and sepsis (n = 19). Two probes of an NIRS device were simultaneously placed on the brachioradialis and deltoid muscles.	21% in-ICU mortality	Non-survivors had rSO_2 values significantly lower than survivors at all times of the study. Both muscles showed consistent discriminatory power for mortality.
Bourcier et al.[29]	Adults from an ICU; Groups: no control group, severe sepsis (n = 40) and septic shock (n = 63). Peripheral perfusion was measured with four temperature gradients, CRT and mottling score.	36% in-ICU mortality	Toe-to-room temperature gradient and its variations are independent predictors of mortality due to multi-organ failure in patients with septic shock. Increased CRT and high mottling score were also predictors of mortality
Houwink et al.[30]	Adults from an ICU; Groups: no control group, septic shock (n = 821). Peripheral perfusion was measured with temperature gradient central-peripheral (Delta T).	26% in-hospital mortality	Delta T at 24 hours, but not at admission, is independently associated with mortality.
Erikson et al.[31]	Adults from an ICU; Groups: no control group and sepsis (n = 31). Retinal blood flow was measured using fluorescein angiography and RAFT.	12% at 30 days	There were no differences in mortality rates between the patients with different retinal blood flow (lower or higher RAFT).
Fontana et al.[32]	Adults from an ICU; Groups: No control group, severe sepsis (n = 27) and septic shock (n = 95). Microcirculation was evaluated using SDF imaging.	43% in-ICU mortality	PPV and MFI were lower in non-survivors than in survivors. These parameters were independent predictors of mortality
Lara et al.[33]	Adults from an ED; Groups: no control group and sepsis (n = 95). Peripheral perfusion assessment was measured by CRT.	63% in-hospital mortality	Hyperlactatemic septic patients with abnormal CRT after initial fluid resuscitation exhibited higher mortality and worse clinical outcomes than patients with normal CRT

Table 3 (*Continued*)

Reference	Methodology	Main results	
		Mortality	Peripheral perfusion *vs* mortality
Macdonald et al.[34]	Adults from an ED; Groups: control group (n = 180) and sepsis (n = 143). Perfusion was assessed by StO_2 using the NIRS method.	7% at 28 days	StO_2 less than 75% at 72 hours after admission was associated with in-hospital mortality/ICU admission, independent of both qSOFA and lactate.

CRT, capillary refill time; ED, emergency department; HbO2, oxygen haemoglobin saturations; ICU, intensive care unit; LDF, laser doppler flowmetry; MFI, microvascular flow index; NIRS, near infrared spectroscopy; OCT, transcutaneous oxygen challenge; OPS, orthogonal polarization spectral; PI, perfusion index; PPV, proportion of perfused small vessels; RAFT, retinal arterial filling time; rSO_2, regional oxygen saturation index; SOFA, sequential organ failure assessment; StO_2, tissue oxygen saturation; VLS, visible light spectroscopy.

Table 4 Timing of evaluation of microcirculation or peripheral perfusion.

Reference	Timing of patient evaluation
De Backer et al.[11]	Was not clearly informed
Sakr et al.[2]	At inclusion and at 24 hours intervals after initial fluid resuscitation, during the circulatory shock
Doerschug et al.[3]	After fluid resuscitation, 24 hours after diagnosis
Trzeciak et al.[12]	During the first 6 hours of fluid resuscitation
Leone et al.[14]	After the macrohemodynamic variables seemed optimal to attending physician (after fluid resuscitation)
Spanos et al.[15]	During the first 6 hours of fluid resuscitation
Sakr et al.[16]	Within first 24 hours of management and at 24 hours intervals, during the circulatory shock
Ait-Oufella et al.[17]	After initial 6 hours of fluid resuscitation
Rodriguez et al.[18]	At ICU admission, 12 and 24 hours after beggining of fluid resuscitation (admission)
Shapiro et al.[19]	Was not clearly informed
Ait-Oufella et al.[20]	After initial 6 hours of fluid resuscitation
Edul et al.[21]	During the first 24 hours after admission after initial management and hemodynamic stabilization
De Backer et al.[22]	Within 24 hours of the onset of sepsis and after 48 hours of the onset of sepsis
He et al.[5]	After fluid resuscitation, after initial 24 hours of management
Hernandez et al.[23]	Within 24 hours of septic diagnosis and fluid resuscitation
Ait-Oufella et al.[24]	After initial 6 hours of fluid resuscitation
Mari et al.[25]	After initial 6 hours of fluid resuscitation and hemodynamic stabilization
Galbois et al.[26]	During and after initial fluid resuscitation (6 hours intervals during the initial 24 hours of management in ICU)
Rasmy et al.[27]	After initial 6 hours of fluid resuscitation
Rodríguez et al.[28]	At ICU admission and 24 hours after beggining of fluid resuscitation (admission)
Bourcier et al.[29]	After initial 6 hours of fluid resuscitation
Houwink et al.[30]	During the first 24 hours after admission
Erikson et al.[31]	During the first 24 hours after admission, 2–5 days later and 3–6 months after the hospital discharge.
Fontana et al.[32]	Median of 2 days after admission – Interquartile range (1–3 days)
Lara et al.[33]	Before and after initial 6 hours of fluid resuscitation
Macdonald et al.[34]	At inclusion and after 3 hours of management

Interestingly, among the found studies that showed no association between mortality and perfusion, 2 of the 3 articles also used NIRS method.[3,19] The remaining article that showed no association used retinal blood flow evaluation.[31] In this study the authors recognized that the sample size was insufficient to detect clinically relevant outcomes. However, it may be that the retinal microvascular bed can not be associated with prognosis.

Another important issue in the interpretation of these results is related to when peripheral perfusion was evaluated. In general, some authors argue that the improved survival prediction resulting from clinical monitoring of

peripheral perfusion may be related to the fact that non-vital vascular beds are among the first to deteriorate and the last to be restored after resuscitation.[7] Conversely, early microcirculatory dysfunctions and early peripheral hypoperfusion (first hours of fluid resuscitation) tend to still be at least partially correlated with systemic circulation (hemodynamic coherence)[7,13] and their prognostic significance is thus more likely to be linked to the effects of the initial macro-hemodynamic resuscitation.[8,13,47,48] In addition, very early evaluation of patients with low severity may not show any significant microcirculatory abnormalities. A study conducted by Filbin et al.[49] in an emergency department using the SDF method in 63 septic patients with low SOFA scores (median: 1) and without hypotension, did not show any measurable microcirculatory flow abnormalities compared to non-infected patients. Even taking these aspects into consideration, the articles selected in this review showed that poor perfusion and microcirculatory abnormalities in peripheral tissues are predictive of mortality, regardless of whether they were evaluated early (13 of 23 articles) or late (10 of 23 articles). However, none of the selected articles undertook early evaluations of low severity septic patients.

Finally, it is important to emphasize that despite the evident association between hypoperfusion in peripheral tissues and higher mortality in septic patients, as was shown in this review, the literature has not yet established a causal relationship. Some authors argue that peripheral hypoperfusion and microcirculatory disturbances may simply be epiphenomena and not themselves trigger the circulatory failure or, at least, directly ''mirror'' the multi-organ failure in sepsis.[6] Therefore, considering the perfusion of peripheral tissues as a ''therapeutic target'' or as a ''causation'' of mortality would still be questionable. However, a recent and important clinical trial began to answer this knowledge gap.[49] The ''Andromeda-Shock trial'' aimed to guide the hemodynamic resuscitation in septic shock based on peripheral perfusion compared to lactate-guided resuscitation. Although the ''perfusion-guided therapy'' had a negative result in this ''superiority study design'', the very similar results between strategies strongly suggests that the peripheral perfusion, on its own, could be considered a ''resuscitation target'' in the shock, at least effective.[50]

This systematic review have limitations. First, i*t was not possible to carry out a meta-analysis* of the evidence from studies because of methodological and statistical heterogeneity between the methods. Second, the studies selected were performed over a period of almost two decades, and sepsis management changed considerably during this period.[1,4] Therefore, a ''treatment bias'' can not be ruled out in the interpretation of the data. Third, it is important to point out that, although heterogeneity and hypoperfusion are related microcirculatory disorders, they do not concern the same phenomenon. Although some methods cited evaluate both disorders (e.g. OPS and SDF) our review aimed to evaluate only the impact of peripheral hypoperfusion (flow reduction of peripheral tissues) on prognosis. Further review is needed specifically addressing microvascular heterogeneity. Lastly, although this review was careful to refer to the time when perfusion was evaluated, data on the peripheral perfusion evolution in each patient were not included in the search strategy. Because of this, we can not draw conclusions about ''serial assessment'' of peripheral perfusion and its impact on prognosis in a systematic way.

In conclusion, among septic patients, the diagnosis of hypoperfusion and microcirculatory abnormalities in non-vital organs was associated with increased mortality in almost all of the studies selected in this review. The association was found regardless of whether they were evaluated early or late in relation to the time of hemodynamic management of sepsis. However, these results still do not establish a causal relation and additional studies must be undertaken to verify if this association can be considered a marker of the gravity or a trigger factor for organ failure and poor prognosis in sepsis.

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Conflicts of interest

The authors declare no conflicts of interest.

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