On Admission, Microcirculation Abnormality is an Independent Predictor of Sepsis and Sepsis-related Mortality: A Hospital-based Study

Anshumalini Panda[1], Gouroumourty Revadi[2], Jai P Sharma[3], Abhijit Pakhare[4], Abhishek Singhai[5], Rajnish Joshi[6], Saurabh Saigal[7]

ABSTRACT

Background: Microcirculatory derangement is the primary cause of organ dysfunction in patients with sepsis. Assessment of the microcirculation is usually done by means of indirect parameters (SvO_2, transcutaneous PO_2, serum lactate). The aim of our study is to understand microcirculatory abnormalities in patients with sepsis by directly visualizing the tiny vessels using hand-held video microscopes (HVMs) and determining the role of this modality in the prediction of sepsis-related mortality.

Methods: A longitudinal prospective hospital-based study was carried out in medical ward and ICU of a tertiary care hospital. Patients admitted with the presumed infectious disease were included. Evaluation of sublingual microcirculation was done in these patients from Day 1 to Day 5. Clinical and laboratory variables and microcirculation variables were compared between patients with or without sepsis and between survivors and non-survivors of sepsis. Chi-square test for categorical and Student's *t*-test or Wilcoxon rank-sum test for continuous variables were applied. Univariate and multivariate regression analyses were performed using the Cox-proportional hazard model.

Results and discussion: On admission, microcirculation assessment measure, PPV (small), was significantly reduced in those with sepsis, as compared to those without sepsis. Multivariable models indicate the inverse relationship of PPV small with mortality.

Keywords: Critically ill adults, Intensivecare, Microcirculation, Sepsis.

Indian Journal of Critical Care Medicine (2022): 10.5005/jp-journals-10071-24110

INTRODUCTION

Sepsis is a life-threatening clinical syndrome caused by dysregulated host response in response to infection.[1] Sepsis is treatable, and timely implementation of targeted interventions improves outcomes.[2] It is estimated by the global burden of disease study that an estimated 48.9 million people develop sepsis annually, 11 million (22%) of whom die. Sepsis-related deaths represent 19.7% of all global deaths, with mortality being highest in low-income countries such as sub-Saharan Africa, Oceania, South Asia, East Asia, and Southeast Asia.[3] Sepsis is an overwhelming host response to toxins released by microorganisms, leading to systemic inflammatory response (SIRS) and with organ dysfunction.[4] Pathophysiology is governed by the release of cytokines that activate the extrinsic coagulation cascade and inhibit fibrinolysis. These overlapping processes result in microvascular thrombosis and poor microcirculatory perfusion, which leads to organ dysfunction.[1]

Microcirculation is defined as the vessels that are devoid of muscular layer, and it commences with arterioles with a diameter of 75 micron and continues through the capillary bed as far as venules with a diameter of 200 micron.[5] Microcirculation is altered within the first three hours after a toxin injection and accelerates in the subsequent 5 hours.[6] It is believed that macrocirculatory effects on peripheral perfusion (such as hypotension and tachycardia) are downstream events in this process.[7] Evaluation of microcirculation has been done indirectly, using indicators of tissue perfusion (such as SvO_2, transcutaneous PO_2, tissue CO_2) or tissue metabolism (serum lactate, troponin T). Urine output is also an indirect, inexpensive, and reliable indicator of tissue perfusion.[8]

[1,5,6]Department of General Medicine, AIIMS, Bhopal, Madhya Pradesh, India

[2,4]Department of Community and Family Medicine, AIIMS, Bhopal, Madhya Pradesh, India

[3,7]Department of Anaesthesiology, AIIMS, Bhopal, Madhya Pradesh, India

Corresponding Author: Saurabh Saigal, Department of Anaesthesiology, AIIMS, Bhopal, Madhya Pradesh, India, Phone: +91 9425301181, e-mail: saurabh.criticalcare@aiimsbhopal.edu.in

Direct bedside assessment of microcirculation has now been made possible using hand-held video microscopes (HVMs) based on the first-generation orthogonal polarization spectral or second-generation side-stream dark-field (SDF) imaging.[9] However, direct microcirculatory abnormalities have been associated with severe sepsis and sepsis-related mortality.[10] It is unclear these are better as compared to traditional predictors. Assessment of microcirculation is still in development and its cutoffs are still undefined.[5] Technical quality and intraobserver variations in image quality remains a concern in current microcirculation assessment methods. A training period is necessary before values are considered a reliable.[11] Since it is an operator-dependent

method, recent guidelines have focused on quality of images obtained by HVMs for a reliable assessment.[12]

We conducted this study to understand microcirculatory abnormalities in patients with sepsis, and the role of this modality in the prediction of sepsis-related mortality. This is the first reported use of microcirculation assessment from India, where we used this bedside technique among patients with fever, with or without sepsis admitted to medical wards and medical intensive care unit of a tertiary care hospital in Central India.

METHODS

Study Design

We conducted a longitudinal hospital-based study among patients presenting with fever and suspected to have sepsis, between January 2018 and August 2019.

Ethics Statement

The study design was approved by the Institutional Human Ethics Committee (IHEC). All participants were included after obtaining a written informed consent.

Setting

This study was conducted at All India Institute of Medical Sciences, Bhopal. Adults with fever usually present either to the medical outpatient department or to emergency services of the hospital. Those who are more seriously ill are admitted to either medical wards or the intensive care unit. At both these locations, treating physicians evaluate patients and record their clinical details, obtain hemodynamic measures, and perform investigations to determine severity. Treating physicians take treatment decisions, which include intravenous fluids, antibiotics, use of inotropes, and other organ-supporting therapies as needed. These details are available in the case-record sheets or monitoring charts of the patients.

Study Definitions

We defined a patient with fever to have a *presumed acute infectious disease* if symptoms were of a short duration (14 days or less), with or without system-specific features of urinary infection (such as increased frequency or burning micturition), respiratory infection (such as cough or dyspnea), skin or soft tissue infection (such as an abscess or cellulitis). Patient was defined to have *sepsis* if there were at least two of four SIRS criteria (fever or hypothermia; tachycardia; hypotension; leukocytosis, or leukopenia) with at least one additional evidence of organ dysfunction (acute kidney injury, hypoxia, thrombocytopenia, altered sensorium, or hepatitis).

Participants

We included all adults admitted to the hospital with a presumed acute infectious disease diagnosis in our study. We included individuals above the age of 18 years, who had duration of illness of two weeks or less, and who satisfied definition of a presumed infectious disease. Study procedures were explained to all such participants or their caregivers. We excluded those patients who denied consent, who were admitted to the hospital for longer than 24 hours before microcirculation assessment is done (as treatments will significantly alter their microcirculation assessment results) or in whom microcirculation assessment was not possible (due to poor mouth opening due to previous oral surgery, presence of trismus, or oral submucosal fibrosis). There were no other study exclusions.

Procedures

Before the start of the study, a study investigator (AP) was trained in use of sublingual microcirculation device. Over a period of two months, she obtained sublingual images that were evaluated in about 100 normal individuals, so as to standardize the methodology and improve the quality of obtained images. All eligible and consenting patients were administered a questionnaire to record their demographic details, and their hospital chart and monitoring sheet was reviewed to record variables that determine the presence or severity of sepsis (temperature, heart/pulse rate, blood pressure, oxygen saturation, leukocyte count, serum lactate levels, platelet count, serum creatinine, blood urea, AST/ALT levels, etc). The available information was used to determine if the patient was in sepsis.

All patients underwent a sublingual microcirculation assessment on the day of admission, using a HVM (Micro-scan, Microvision medical, Amsterdam, Netherlands) based on SDF technology. The device probe is a phase-contrast microscope, connected to a lap-top to visualize the images and ensure that properly focused images are obtained. It allows microcirculation assessment at the bedside. This device uses a probe that is placed below the tongue, a process similar to obtaining an oral temperature reading. The probe has a diameter of 8 mm and is covered with a disposable sheath. The device probe is kept below the tongue so as to visualize the capillary network. Once images are acquired, the probe is removed and device software analyzes the images. Automated Vascular Analysis software (AVA 4.3 C Microscan software Microvision medical, Amsterdam, Netherlands) is used for analysis, based on internationally accepted consensus scoring guidelines. The software identifies the small- and large-sized capillaries from the image and assesses if these are perfused or not perfused. Based on this assessment, we obtained the proportion of all perfused vessels (PPV %), proportion of perfused vessels-small (PPV small %), density of vessels (De Backer density) all, and density of vessels (De Backer density–DBD) small. De Backer score is calculated in the following way: The image is divided by three vertical and three horizontal lines; the De Backer score is calculated as the number of vessels crossing the lines divided by the total length of the lines. The De Backer score was calculated using the same software.

Microcirculation of all participants was evaluated daily for the first three days of hospital admission, to document any changes form baseline. Hospital records were used to determine the complications, mortality, and discharge from the hospital. Among patients with sepsis, the outcome was mortality from sepsis during hospital stay.

Sample Size

Our *apriori* sample size estimates were based on assumptions that of all patients with an infectious disease condition who are admitted to the hospital, about 15% will develop sepsis. Of all patients with sepsis, about 40–60% may not recover. Further, it is estimated that PPV small % is likely to be greater than 75% in those without sepsis, and less than 50% in those with established sepsis. Given these assumptions, we had planned to obtain a logistically feasible sample size of about 120 individuals without sepsis (so as to have at least 30 individuals with an outcome of sepsis) for the first research question, and a logistically feasible sample size of at least 100 individuals with sepsis. To estimate difference in PPV percentage among patients with sepsis who died and who survived, with power of 80%, Type I error of 5% and large effect size of at least 30 individuals in

each group would be required. Therefore, we continued enrollment till a size of 30 was achieved in those who died.

Statistical Analysis

The study variables were collected on a structured data collection form as either continuous or dichotomous variables. The data was entered on Microsoft Excel, and after data cleaning analyzed using IBM Statistical Package for Social Sciences (SPSS) Version 26 software. We compared demographic, clinical, laboratory, and microcirculation variables of individuals with or without sepsis on admission to the hospital. We used Chi-square test for dichotomous variables and Student's *t*-test or Wilcoxon rank-sum test for continuous variables to compare proportions, means, or medians, respectively. We used a *p* <0.01 as a significance level for these comparisons. We evaluated the proportion of those with fever, and who developed sepsis during hospital stay as an outcome. In those with sepsis, we compared demographic, clinical, laboratory, and microcirculation variables of individuals who had a mortality, with those who did not have a mortality due to sepsis. We performed a univariate and a multivariate regression using the Cox-proportional hazard (PH) model to determine the role of microcirculation as a predictor of mortality.

RESULTS

Of a total of 258 eligible and consenting patients who have a microcirculation assessment done on admission, we included 249 in the current study, as their follow-up information was available. Of these, 124 (49.7%) had sepsis and the remaining 125 (50.2%) had an infectious disease diagnosis, and did not have sepsis (Flowchart 1, Table 1). Distribution of infectious disease etiology is shown in Supplementary Table 1. Patients who did not have sepsis were younger, were more likely to be admitted in medical ward, had a lower pulse rate, and had higher oxygen saturation. As expected, those with sepsis had higher serum creatinine, higher leukocyte counts, and lower hemoglobin levels (Table 1). Of 124 participants, those who had sepsis on admission 33 (26.6%; 95% CI 19.6–35.0%) died. Non-survivors were more likely to have been treated in an intensive care unit, had higher pulse rate, and had higher on-admission quick sequential organ functional assessment (qSOFA) scores. These features imply that those who suffer mortality are more seriously ill, but their on-admission biochemical, hematological, and blood-gas values are similar to those who survive (Table 2).

On admission, microcirculation assessment measure proportion of perfused vessels (small) was significantly reduced in those with sepsis, as compared to those without sepsis. This measure was also consistently reduced in those with sepsis who had a mortality, as compared to those who survived. Reduction in this variable was consistent over the first four days of hospital stay (Table 3). Mean De Backer density of large and small vessels, however, was also consistently higher in those with sepsis and in those who had a mortality.

We used the Cox-PH model to identify the predictors of mortality among those having sepsis. In this model, we identified the hazard ratio which is associated with each of the several independent variables to the outcome, which is elapsed time to an event. Here, the event refers to mortality from sepsis and time refers to days since admission to the death/40 days. Results are shown in Table 4. Based on the results of univariate analysis and clinical relevance, we included age, gender, duration of fever, and admission in ICU on Day 1 along with PPV small as independent predictors of mortality. We performed the forward stepwise Cox-PH regression. However, since value of eight persons for PPV small was not available for Day 0, two models were analyzed: One in which independent variable entered was PPV small for Day 0 (115 observations) and other in which independent variable entered was PPV small for Day 1 (123 observations). Multivariable models indicate the inverse relationship of PPV small with mortality independent of admission in ward or ICU, age, gender, and duration of fever (Table 4). It was found that the Cox-PH model 1 has a better diagnostic potential with area under the curve (AUC) of 80.7% as compared to the parameter (100-PPV small 1) with AUC of 72.3%, and the results were statistically significant (*p* <0.001) (Fig. 1).[13]

DISCUSSION

In the current study, we found that individuals who had sepsis were older, had higher pulse rates, elevated serum creatinine, higher leukocyte counts, lower hemoglobin levels, and lower oxygen saturation as compared to those without sepsis. These findings are anticipated as these are defining features of sepsis. Those who died also had a higher pulse rate, higher serum lactate levels, and elevated $PaCO_2$ levels as compared to those who did not survive. Of microcirculation-related variables, PPV small was significantly lower in those with sepsis (as compared to those without sepsis) and in those with sepsis-related mortality (as compared to survivors). It was a significant independent predictor of mortality. In contrast, DBD overall and for small vessels was higher in those with sepsis and those with mortality, but the proportion of perfused vessels was lower. This implies that this density was largely contributed by non-perfused vessels. However,
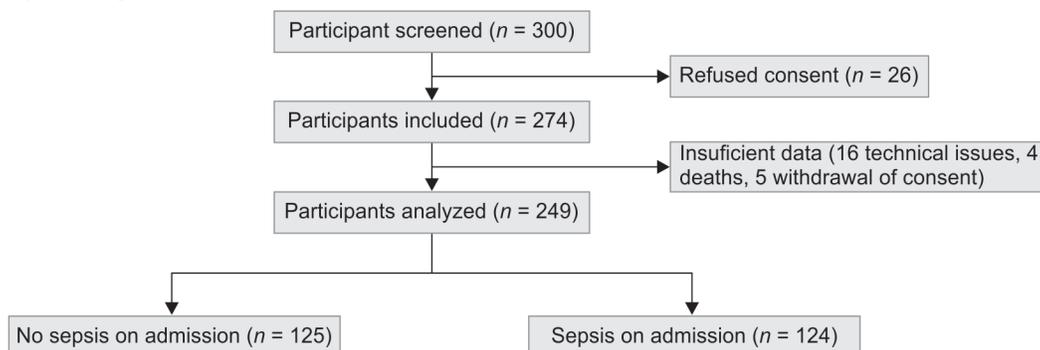
Flowchart 1: Study flow diagram

Table 1: Distribution of variables in those with sepsis and those without sepsis at baseline (*n* = 249)

Variable	Sepsis	No sepsis	p value
Number	*n* = 124	*n* = 125	
Mean age* (SD)	47.92 (18.6)	39.01 (18.12)	<0.001
Female gender# *n* (%)	60 (53.1)	53 (46.9)	0.343
Mean duration of fever in days* (SD)	8.4 (4.64)	8.6 (5.14)	0.805
Initial admission location#			
Ward *n* (%)	23 (16.8)	114 (83.2)	<0.001
High dependency unit *n* (%)	32 (97)	10 (30)	
Intensive care unit *n* (%)	69 (98.6)	1 (1.4)	
On admission clinical variables*			
Mean SBP in mm Hg (SD)	108.73 (20.81)	111.5 (15.2)	0.235
Mean DBP in mm Hg (SD)	65.22 (13.15)	70.34 (12.66)	0.002
Mean pulse rate (SD)	102.35 (18.32)	90.55 (16.33)	<0.001
Mean respiratory rate (SD)	23.9 (6.30)	20.01 (5.07)	0.004
Mean oxygen saturation (SD)	95.31 (5.13)	96.8 (2.37)	<0.001
On admission biochemical variables			
Median serum creatinine$ mg/dL (SD)	1.26 (0.87–2.43)	0.90 (0.74–1.04)	<0.001
Median urea$ mg/dL (SD)	56 (34–100.75)	26 (20.5–37.0)	<0.001
Median ALT level$ (SD)	56 (35–120)	54 (22.6–90.4)	0.067
Median AST level$ (SD)	72 (38.5–132.5)	63 (33.2–108.5)	0.087
Mean Na level* (SD)	132.42 (8.40)	131.59 (4.90)	0.34
Mean K level* (SD)	4.08 (0.69)	4.04 (0.58)	0.607
Median Hb level$ (SD)	10.65 (9.05–12.6)	11.8 (10.6–13.45)	<0.001
Median WBC count$ (SD)	15,615 (11,942–21,910)	9,330 (4,870–15,425)	<0.001
Median platelet count$ (SD)	188,000 (80,750–332,500)	211,006 (92,500–328,000)	0.996

Test of significance used *unpaired *t*-test, #Chi-square test, $Mann–Whitney test

Table 2: Distribution of variables in those with sepsis survivors and non-survivors (*n* = 124)

Variable	Survivors	Non-survivors	p value
Number	91	33	
Mean age* (SD)	49.14 (18.02)	44.54 (18.02)	0.225
Female gender# *n* (%)	45 (75)	15 (25)	0.694
Mean duration of fever in days$ (SD)	7 (5–10)	7 (6–14)	0.07
Initial admission location#			
Ward *n* (%)	22 (24.1)	1 (3.23)	0.009
High dependency unit *n* (%)	25 (27.2)	7 (22.5)	
Intensive care unit *n* (%)	44 (48.3)	25 (80.65)	
On admission clinical variables*			
Mean SBP in mm Hg (SD)	108.89 (22.34)	108.27 (16.16)	0.867
Mean DBP in mm Hg (SD)	66.03 (13.98)	62.96 (10.39)	0.192
Mean pulse rate (SD)	99.60 (14.59)	109.90 (15.42)	0.003
Mean respiratory rate (SD)	24.05 (6.71)	23.78 (5.01)	0.19
Mean oxygen saturation (SD)	95.60 (5.6)	94.5 (3.5)	0.020
On admission biochemical variables			
Mean serum creatinine* mg/dL (SD)	1.25 (0.86–2.18)	1.5 (0.89–3.08)	0.271
Mean urea$ mg/dL (SD)	55 (31–99)	68 (44–112)	0.086
Mean ALT level$ (SD)	54 (35.5–104)	81 (31.7–334)	0.088
Mean AST level$ (SD)	68 (38.5–107)	39.7 (9.5–244.5)	0.242

(Contd...)

Table 2: (*Contd...*)

Variable	Survivors	Non-survivors	p value
Mean Na level* (SD)	132.14 (8.76)	133.18 (7.39)	0.545
Mean K level* (SD)	4.09 (0.72)	4.08 (0.62)	0.936
Mean Hb level$ (SD)	10.7 (9.2–12.6)	10.5 (10.5–12.6)	0.663
Mean WBC count$ (SD)	15400 (10970–19870)	17800 (13250–24740)	0.108
Mean platelet count$ (SD)	208,000 (114,000–345,000)	123,000 (66,000–292,500)	0.044
On admission blood gas variables			
Mean HCO_3* (SD)	20.45 (5.93)	18.97 (4.62)	0.252
Mean $PaCO_2$$ (SD)	34 (29.75–42)	41 (34.7–118.5)	0.009
Mean lactate$ (SD)	2.4 (1.2–3.5)	4.5 (3.0–5.2)	0.038
Mean PaO_2* (SD)	86.27 (26.44)	77.68 (19.86)	0.135
Mean qSOFA score (SD)	1.77 (0.96)	2.66 (0.47)	<0.001
Primary cause of sepsis			
Respiratory	42 (46.15)	18 (58.06)	
CRBSI	21 (23.08)	6 (19.35)	
Urosepsis	19 (20.88)	2 (6.45)	
SSTI	0 (0)	1 (3.45)	
Unknown	4 (9.89)	6 (19.35)	

Test of significance used *unpaired *t*-test, #Chi-square test, $Mann–Whitney test

Table 3: Microcirculation assessment in those with sepsis and with sepsis mortality (*n* = 249)

Variable	No sepsis	Sepsis	Sepsis survivors	Sepsis mortality
Number	n = 125	n = 124	n = 91	n = 33
Mean proportion of perfused vessels				
Day 0	82.52 (13.12)	77.98 (14.43)	80.33 (13.34)	71.89 (15.58)*
Day 1	84.94 (12.28)	77.72 (14.45)#	80.03 (13.25)	71.13 (16.90)*
Day 2	84.80 (12.14)	83.44 (40.92)	81.70 (12.30)	88.41 (78.50)*
Day 3	89.5 (80–93)	78.00 (15.50)	80.67 (14.6)	71.6 (16.21)*
Mean proportion of perfused vessels (small)				
Day 0	81.14 (22.75)	68.79 (25.69)#	74.15 (24.36)	54.87 (24.09)*
Day 1	80 (75–100)	75 (50–80)#	71.62 (22.72)	54.60 (20.22)*
Day 2	80 (75–95)	75 (50–80)#	72.58 (17.95)	57.67 (20.81)*
Day 3	83 (75–96)	74 (50–80)#	73.14 (18.16)	53.64 (17.95)*
Mean De Backer density				
Day 0	3.01 (0.96)	3.00 (2.34, 3.38)#	2.78 (2.09–3.29)	3.2 (2.42–3.84)
Day 1	3.17 (0.85)	3.11 (2.32, 3.66)#	2.87 (2.2–3.56)	3.4 (3.09–4.32)*
Day 2	3.08 (0.96)	2.87 (2.33, 3.46)#	2.67 (2.09–3.44)	3.03 (2.67–4.0)*
Day 3	2.99 (0.97)	3.11 (2.55, 3.97)#	3.00 (2.33–3.65)	3.57 (2.83–4.1)
Mean De Backer density (small)				
Day 0	0.15 (0.18–0.34)	0.34 (0.19–0.54)#	0.27 (0.12–0.45)	0.54 (0.36–0.87)*
Day 1	0.21 (0.10–0.28)	0.32 (0.19–0.48)#	0.26 (0.13–0.38)	0.5 (0.27–0.78)*
Day 2	0.22 (0.10–0.29)	0.29 (0.23–0.47)#	0.25 (0.22–0.43)	0.41 (0.34–0.78)*
Day 3	0.21 (0.12–0.28)	0.29 (0.22–0.49)#	0.24 (0.18–0.34)	0.55 (0.36–0.78)*

#These variables in those with sepsis were significantly different as compared to those without sepsis (*p* <0.001).
*These variables in those with sepsis mortality were significantly different as compared to those who survived (*p* <0.001)

previous studies conducted in Europe and North America have suggested that poor sublingual microcirculation measured by HVMs is an independent predictor of mortality and is associated with a poor organ perfusion.[12] Our study, first from a low-middle-income setting also reports that patients with sepsis have a poor perfusion of small vessels in microcirculation. Among those with sepsis, microcirculation is further reduced on admission in non-survivors.

Table 4: Cox-PH regression for predictors of mortality

| Variable	n	Unadjusted				Adjusted			
		Model coeff.	HR	95% CI of HR	p value	Model coeff.	HR	95% CI of HR	p value
Age	124	−0.013	0.987	0.969–1.006	0.180				
Gender	124	0.047	1.048	0.744–1.477	0.788				
Fever duration	124	0.062	1.064	0.999–1.134	0.054				
ICU vs Ward	124	1.587	4.888	2.016–11.851	<0.001	1.5|1.45[(Model-2)]	4.52|4.27	1.85–11.02| 1.62–11.25	0.009|0.003
SBP	124	−0.001	0.999	0.983–1.015	0.885				
DBP	124	−0.016	0.984	0.958–1.011	0.238				
RR	124	−0.004	0.996	0.944–1.050	0.872				
S. creatinine	123	0.308	1.360	1.047–1.768	0.021				
SpO_2	124	−0.024	0.977	0.936–1.020	0.283				
ALT	121	0.000	1.000	1.00–1.001	0.060				
Hemoglobin	124	−0.030	0.970	0.852–1.106	0.651				
Platelets	124	0.000	1.000	1.00–1.00	0.095				
HCO_3	88	−0.043	0.958	0.890–1.030	0.247				
pH	88	−5.137	0.006	0.00–0.099	<0.001				
$PaCO_2$	68	0.016	1.016	1.002–1.030	0.230				
PaO_2	88	−0.014	0.986	0.968–1.005	0.140				
Blood culture	89	−0.306	0.736	0.294–1.845	0.514				
Chest X-ray	115	−0.199	0.819	0.400–1.679	0.586				
PPV0	115	−0.026	0.974	0.956–0.993	0.006				
PPV1	123	−0.030	0.971	0.952–0.990	0.003				
PPV small 0	115	−0.023	0.977	0.964–0.990	<0.001	−0.019[(Model-2)]	0.981	0.967–0.995	0.009
PPV small 1	123	−0.024	0.976	0.963–0.990	0.001	−0.023	0.97	0.964–0.991	0.001
PPV 10% fall	95	0.039	1.040	0.487–2.22	0.919				
PPV 20% fall	95	0.512	1.660	0.676–4.110	0.266				
De Backer day 0	115	0.273	1.314	0.92–1.878	0.134				
De Backer day 1	123	0.692	1.990	1.390–2.860	<0.001				
De Backer small day 0	115	0.228	9.850	3.70–26.22	<0.001				
De Backer small day 1	122	1.840	6.290	2.490–15.85	<0.001				
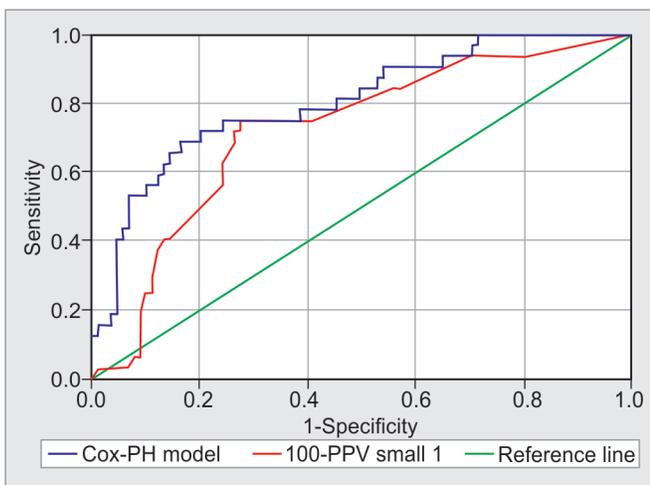
Fig. 1: ROC curve for the Cox-PH model

Microcirculation assessment technology has evolved. The first-generation devices used orthogonal polarized spectroscopy (OPS). Second-generation devices have used a side-stream dark-field (SDF) imaging.[12] We have used a second-generation device in our study. Currently, third-generation devices using incident dark-field (IDF) technology are also available, which have further improved image quality.[12] However, the previous standards of microcirculation assessment were reported as a round-table in 2007.[9] These have recently been revised as a 2018 consensus statement. More recent guidelines have emphasized the specific set of measurements that need to be taken, as well as quality indicators in image acquisition.[12] However, these guidelines were not available when we planned our study, yet we had incorporated some of the principles in our study. First, training of a person performing microcirculation is important, and the trainee captured images on patients on mechanical ventilation so that hand gets accustomed to capture stable images. First, we captured only those images that have flowing RBCs in the larger vessels. Second, the software we used only interprets artifact-free images. We did not use any image quality scoring, as it was not available in the software we are using. We used PPV and De Backer density as two indicators of microcirculation perfusion and vessel density in our study. These are two objective measures that are calculated by the software. We did not measure the other two recommended parameters—microvascular flow index (MFI) and the heterogeneity index (HI)—as these guidelines were not

available at the time of planning our study. MFI is a subjective assessment of type of flow in each quadrant of the image, and it is anticipated that sluggish flow is a hallmark of poor perfusion. HI is a measure of variability and indicates a ratio of highest and a lowest value of PPV or MFI. We can measure these additional variables in future studies.

Macrocirculation in large vessels behaves differently as compared to microcirculation in smaller vessels. Various software-based tools are available to interpret sublingual microcirculation[14] vessels. Peripheral perfusion an indicator of microcirculation was compared with microcirculation in a recent study from China.[10] The authors evaluated the change in proportion of perfused small sublingual vessels at 6 hours (δPPV), and peripheral perfusion index (PI) as predictors of poor prognosis in sepsis. Based on this assessment, they divided 74 participants into four groups: (a) high PI and high δPPV, (b) high PI and low δPPV, (c) low PI and high δPPV, and (d) low PI and low δPPV. SOFA scores were highest in the last group.[10]

In a systematic review of pharmacological interventions targeting microcirculation, it was suggested that conventional inotropic drugs such as noradrenaline, or dobutamine, do not improve microvascular flow.[15] Vasodilators such as nitrates also have a modest effect on microcirculation.[15] On the other hand, the addition of vasopressin, or terlipressin, to noradrenaline or the use of levosimendan maintained microcirculatory flow.[15] Passive leg raising does not improve microcirculation among patients with septic shock.[16] This is an emerging area, and beyond initial pilot studies, mortality benefits of such pharmacological alterations in microcirculation have not been demonstrated.

Alternate modalities of microcirculation assessment are thermal challenge tests, biomarkers of glycocalyx degradation, and veno-arterial differences in $PaCO_2$.[5] Deterioration of the endothelial glycocalyx (eGC), a protective carbohydrate-rich layer lining the luminal surface of the endothelium, plays a key role in vascular barrier dysfunction and eventually organ failure in systemic inflammatory response syndrome and sepsis.[6] It is feasible to measure endothelial glycocalyx using side-stream microcirculation assessment, and it could be a future application of sublingual microcirculation assessment.[6] In severe trauma, many indirect measurements of perfusion do not correlate with microvascular perfusion. However, visualized perfusion deficiencies do reflect a shift toward anaerobic metabolism.[14] More detailed assessments of such a compromise in patients with trauma are currently being evaluated.[16]

Limitations

Use of microcirculation technology is challenging. In terms of technical feasibility, these studies may be performed in non-intubated and intubated patients. It is feasible to obtain measurements in non-intubated patients who are conscious, and cooperate for the procedure. If the non-intubated patient is irritable, or unstable, it becomes difficult to perform the measurement. In a pediatric study,[17] sublingual microcirculation was not feasible in the majority of unstable patients. In contrast, intubated patients are sedated and cooperativeness becomes less of an issue. In a recent pediatric feasibility study,[17] measurements were difficult in unstable intubated patients as well. While in this study only 18 full measurements could be obtained from a total of 102 eligible participants, in our study non-measurement due to feasibility issues was much lower. We have not used MFI and HI, which would have been better indicators of flow measurement as compared to PPV and De Backer density.

This study itself was a learning curve for us, and it's just a stepping stone where we were just able to identify a subset of patients in whom microcirculatory changes correlated with organ failures. These microcirculatory changes correlated with clinical outcomes were not in the scope of the study but up next we are given fluid challenges and seeing whether it improves microcirculatory perfusion, or the addition of inotrope in cardiogenic shock improves microcirculatory perfusion. Regarding cost-effectiveness, it is an issue but best thing its non-invasive and just can cater to a large number of patients at single point of time.

Conclusion

Sepsis is a life-threatening condition. It is therefore important to predict its course outcome. Outcome is directly related to the state of perfusion in microcirculation as it is the ultimate source of nutrient and oxygen for end organs. In our study, we tried to visualize the microcirculation directly with hand-held video microscope and found that admission microcirculation assessment measure, PPV (small), was significantly reduced in those with sepsis, as compared to those without sepsis. Multivariable models indicated an inverse relationship of PPV small with mortality. Thus, we concluded from the study that a serial sublingual microcirculation assessment can help in the prediction of sepsis. Although it could not predict mortality earlier or better than the most traditional scoring system like SOFA, qSOFA, APACHE which are combinations of multiple clinical and laboratory parameters, sublingual microcirculation assessment is the single most important and direct indicator of tissue perfusion status if compared head-on with individual parameters.

Availability of Data and Materials

The datasets generated during and/or analyzed during the present study are not publicly available, owing to further research based on this dataset, but they are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study design was approved by the Institutional Human Ethics Committee (IHEC). All participants were included after obtaining a written informed consent.

Authors Contribution

Data curation, investigation, writing—Anshumalini Panda. Statistics—G Revadi. Conceptualization, writing, review, editing, statistics—Rajnish Joshi. Statistics, review, editing, writing—Abhijit Pakhare. Writing, Review, editing—Saurabh Saigal. Review, editing—JP Sharma. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Orcid

Anshumalini Panda https://orcid.org/0000-0003-2916-0086
Gouroumourty Revadi https://orcid.org/0000-0002-9646-4971

Jai P Sharma ⦿ https://orcid.org/0000-0003-4147-1637
Abhijit Pakhare ⦿ https://orcid.org/0000-0003-2897-4141
Abhishek Singhai ⦿ https://orcid.org/0000-0002-3216-3387
Rajnish Joshi ⦿ https://orcid.org/0000-0001-9201-3914
Saurabh Saigal ⦿ https://orcid.org/0000-0002-2364-2271

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). Journal of the American Medical Association 2016;315(8):801–810. DOI: 10.1001/jama.2016.0287.
2. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock—2016. Crit Care Med 2017;45(3):486–552. DOI: 10.1097/CCM.0000000000002255.
3. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395(10219):200–211. DOI: 10.1016/S0140-6736(19)32989-7.
4. Rudd KE, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, et al. The global burden of sepsis: barriers and potential solutions. Crit Care 2018;22(1):232. DOI: 10.1186/s13054-018-2157-z.
5. De Backer D. Is microcirculatory assessment ready for regular use in clinical practice? Curr Opin Crit Care 2019;25(3):280–284. DOI: 10.1097/MCC.0000000000000605.
6. Pranskunas A, Pilvinis V, Dambrauskas Z, Rasimaviciute R, Planciuniene R, Dobozinskas P, et al. Early course of microcirculatory perfusion in eye and digestive tract during hypodynamic sepsis. Crit Care 2012;16(3):R83. DOI: 10.1186/cc11341.
7. Sharawy N, Mahrous R, Whynot S, George R, Lehmann C. Clinical relevance of early sublingual microcirculation monitoring in septic shock patients. Clin Hemorheol Microcirc 2018;68(4):347–359. DOI: 10.3233/CH-170244.
8. Naumann DN, Mellis C, Husheer SL, Hopkins P, Bishop J, Midwinter MJ, et al. Real-time point of care microcirculatory assessment of shock: design, rationale and application of the point of care microcirculation (POEM) tool. Crit Care 2016;20(1):310. DOI: 10.1186/s13054-016-1492-1.
9. De Backer D, Hollenberg S, Boerma C, Goedhart P, Büchele G, Ospina-Tascon G, et al. How to evaluate the microcirculation: report of a round table conference. Crit Care 2007;11(5):R101. DOI: 10.1186/cc6118.
10. Pan P, Liu DW, Su LX, He HW, Wang XT, Yu C. Role of combining peripheral with sublingual perfusion on evaluating microcirculation and predicting prognosis in patients with septic shock. Chin Med J (Engl) 2018;131(10):1158–1166. DOI: 10.4103/0366-6999.231524.
11. Sallisalmi M, Oksala N, Pettilä V, Tenhunen J. Evaluation of sublingual microcirculatory blood flow in the critically ill. Acta Anaesthesiol Scand 2012;56(3):298–306. DOI: 10.1111/j.1399-6576.2011.02569.x.
12. Ince C, Boerma EC, Cecconi M, De Backer D, Shapiro NI, Duranteau J, et al. Second consensus on the assessment of sublingual microcirculation in critically ill patients: results from a task force of the European Society of Intensive Care Medicine. Intensive Care Med 2018;44(3):281–299. DOI: 10.1007/s00134-018-5070-7.
13. Cox D. Regression models and life-tables. J R Stat Soc Ser B (Methodological) 1972;34(2):187–220. DOI: 10.1007/978-1-4612-4380-9_37 [Retrieved June 23, 2021]. Available from: http://www.jstor.org/stable/2985181.
14. Trzeciak S, McCoy JV, Phillip Dellinger R, Arnold RC, Rizzuto M, Abate NL, et al. Microcirculatory Alterations in Resuscitation and Shock (MARS) investigators. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med 2008;34(12):2210–2217. DOI: 10.1007/s00134-008-1193-6.
15. Potter EK, Hodgson L, Creagh-Brown B, Forni LG. Manipulating the microcirculation in sepsis – the impact of vasoactive medications on microcirculatory blood flow: a systematic review. Shock 2019;52(1): 5–12. DOI: 10.1097/SHK.0000000000001239.
16. Pinheiro TT, de Freitas FGR, Coimbra KTF, Mendez VMF, Rossetti HB, Talma PV, et al. Short-term effects of passive mobilization on the sublingual microcirculation and on the systemic circulation in patients with septic shock. Ann Intensive Care 2017;7(1):95. DOI: 10.1186/s13613-017-0318-x.
17. González R, López J, Urbano J, Solana MJ, Fernández SN, Santiago MJ, et al. Evaluation of sublingual microcirculation in a paediatric intensive care unit: prospective observational study about its feasibility and utility. BMC Pediatr 2017;17(1):75. DOI: 10.1186/s12887-017-0837-5.