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Association of Sublingual Microcirculation Parameters and Capillary Refill Time in the Early Phase of ICU Admission*

Weipeng Huang, MD[1,2]
Hui Xiang, MD[1,2]
Chang Hu, MD[1,2]
Tong Wu, MD[1,2]
Dandan Zhang, MD[1,2]
Siqing Ma, MD[3]
Bo Hu, MD[1,2]
Jianguo Li, MD[1,2]

OBJECTIVES: This observational study was conducted to investigate capillary refill time (CRT) during the early phase of ICU admission in relationship with microvascular flow alteration and outcome in critically ill patients.

DESIGN: Prospective, observational, pilot study.

SETTING: ICU in a university hospital.

PATIENTS: Two hundred eighty-two critically ill adult patients admitted to the ICU.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: All patients underwent simultaneous measurements by CRT and sidestream dark field imaging within 24 hours of ICU admission. Other clinical data such as demographic characteristics, hemodynamics, laboratory values, treatment, and physiologic parameters were also included simultaneously. Microcirculatory measurements were performed at 10.2 ± 5.7 hours after ICU admission. Of the 282 included patients, 106 (37.6%) were female, the median (interquartile range) age was 63 years (53–74 yr), and the median Sequential Organ Failure Assessment (SOFA) score was 5 (2–7). The primary finding was the association between CRT and simultaneous the condition of peripheral circulation (microvascular flow index [MFI]: $r = -0.4430$, $p < 0.001$; proportion of perfused vessels: $r = -0.3708$, $p < 0.001$; heterogeneity index: $r = 0.4378$, $p < 0.001$; perfused vessel density: $r = -0.1835$, $p = 0.0020$; except total vessel density: $p = 0.9641$; and De Backer score: $p = 0.5202$) in critically ill patients. In addition, this relationship was also maintained in subgroups. Microcirculatory flow abnormalities, 28-day mortality, and SOFA score appeared to be more severe for increasing CRT. In a multivariable analysis, prolonged CRT was independently associated with microvascular flow abnormalities (MFI < 2.6; odds ratio [OR], 1.608; 95% CI, 2.1–10.2; $p < 0.001$). Similarly, multivariable analysis identified CRT as an independent predictor of 28-day mortality (OR, 1.296; 95% CI, 1.078–1.558; $p = 0.006$).

CONCLUSIONS: In our ICU population, a single-spot prolonged CRT was independently associated with abnormal microcirculation and increased mortality.

KEY WORDS: capillary refill time; intensive care unit; microcirculation; sidestream dark field microscopy

Capillary refill time (CRT) is defined as the time required to restore skin color after whitening caused by applying pressure to the distal capillary bed (1). CRT has been used as an indirect tool to monitor peripheral perfusion in critically ill patients. Recent studies demonstrate goal-directed therapy protocols based on CRT assessment have been shown not inferior or even superior to lactate-targeted resuscitation (2, 3). The latest surviving sepsis campaign guidelines suggest using CRT to guide resuscitation as an adjunct to other measures of perfusion in adults with septic shock (4).

*See also p. 977.

DOI: 10.1097/CCM.0000000000005851

KEY POINTS

Question: What extent capillary refill time (CRT) is correlated with microcirculatory abnormalities?

Findings: This prospective, observational study demonstrated that CRT was significantly related to microcirculatory blood flow parameters (microvascular flow index [MFI]: $r = -0.4430$; proportion of perfused vessels [PPV]: $r = -0.3708$; and heterogeneity index [HI]: $r = 0.4378$) in critically ill patients, and this relationship was also maintained in subgroups. Multivariable analysis identified CRT as an independent predictor of abnormal microcirculation (MFI < 2.6) and 28-day mortality.

Meaning: CRT was correlated with the condition of peripheral perfusion (MFI, PPV, HI) in critically ill patients and independently associated with abnormal microcirculation and increased mortality.

However, the utility of CRT in the management of critically ill patients is still a matter of debate. Most of these studies have concentrated on the advantages of CRT to guide resuscitation and failed to show any relationship with microcirculatory alternation in critically ill patients. For example, van Genderen et al (5) reported the use of peripheral perfusion parameters (including CRT) as resuscitation target may avoid the risk of fluid overload. Franzosi et al (6) observed early improvement in hemodynamic and skin perfusion parameters (including CRT) was associated with success in nutrition therapy.

Critically ill patients have been associated with microcirculatory alterations (7) and these in turn with the development of organ failure and poor outcome (8–10). Therefore, early detection of microcirculatory alterations is important to design prompt treatment, avoiding further organ damage and poor outcome. Sidestream dark field (SDF) imaging (11) can directly visualize microvascular tissue perfusion in critically ill patients. Using a handheld noninvasive sublingual video microscope researchers can observe and analyze the alternations of peripheral capillary perfusion and RBC flow velocity directly (12).

Since no investigations exist as to what extent CRT is correlated with microcirculatory abnormalities, we conducted an observational study to evaluate the association between CRT, microcirculatory flow and outcome in critically ill patients during the early phase of ICU admission.

MATERIALS AND METHODS

This study took place from October 2021 to January 2022 in the ICU of Zhongnan Hospital of Wuhan University. We performed in accordance with the Declaration of Helsinki. All experiments were performed in accordance with relevant named guidelines and regulations. The study was approved by the Medical Ethics Committee of Zhongnan Hospital of Wuhan University (2021078) on October 10, 2021. The study was registered on November 7, 2021, ChiCTR2100052999.

Inclusion and Exclusion Criteria

We enrolled consecutive adult critically ill patients within 24 hours of ICU admission that had undergone initial resuscitation and stabilization. The microcirculation measurement was performed within 24 hours of ICU admission after hemodynamic stabilization was achieved (mean arterial pressure [MAP] > 65 mm Hg, and no change in vasopressor use for 2 hr). Exclusion criteria were pregnancy, multiple ICU admission (only included for the first time), patients with peripheral vascular disease, ineligible for microcirculatory assessment, and inability to obtain high-quality SDF images. Each enrolled patient or relative provided written informed consent.

Data Collection

All microcirculation assessments were performed after 2 hours of hemodynamic stability time. The following data were collected simultaneously with the assessment of microcirculation: demographic variables, comorbidities, focus of infection, hemodynamics, laboratory values, vasopressor dose (13), and score parameters, including the Sequential Organ Failure Assessment (SOFA) score (14) and Acute Physiology and Chronic Health Evaluation (APACHE) II score (15). At ICU discharge, renal replacement therapy, length of ICU stay, and hospital mortality were also documented.

Assessment of Sublingual Microcirculation

The researchers (W.H., H.X., T.W.) attended a microcirculation training course (16) to master the operation

of SDF imaging device (Medsoft System, Guangzhou, China). The sublingual microcirculation was visualized using an SDF imaging device. After gently wiping the patient's oral secretions with gauze, the tip of the microscope was gently placed on the lateral side of the tongue covering an area of approximately 2.5–4.0 cm^2. At each measurement, we adjusted the light intensity and focus, until the best quality of the video was obtained. Finally, we respectively recorded five videos from different adjacent mucosa (17). Based on the method described by Massey et al (18) (even illumination across the entire vision, an analyzable video clip is ≥ 5 s, good focus for vessels, video without occlusions, video recording is stable, no pressure artifacts), we evaluated the objective quality score of images, and poor-quality images were discarded.

Based on the consensus conference (19), two well-trained researchers (H.X., T.W.), who were blinded to the clinical condition of patients, performed computer-assisted analysis (AVA 3.0 software; MicroVision Medical, Amsterdam, The Netherlands). The microvascular flow index (MFI) was computed as the mean of the predominant flow classification of small vessels over the four quadrants of the video screen. (0 = absent flow; 1 = intermitted flow; 2 = sluggish flow; 3 = continuous flow). The abnormal microcirculatory flow was defined as MFI less than 2.6 (20). Additionally, the total vessel density (TVD), the perfused vessel density (PVD), the proportion of perfused vessels (PPV), the heterogeneity index (HI), and De Backer score were calculated, as described in **Supplemental Table 1** (http://links.lww.com/CCM/H317) (16). All parameters of sublingual microcirculation were reported from small vessel analysis (< 20 μm in diameter), which is the principal site for nutrition and oxygen exchange between underlying tissues and blood (21).

Assessment of CRT

CRT measurements were performed using a glass microscope slide to apply pressure to the ventral surface of the right index distal phalanx according to the method described by Hernandez et al (2). The pressure was increased until the skin turned white, then held for 10 seconds. After researchers released the pressure, the time for return of the normal skin color was CRT. The CRT assessment was performed immediately after the SDF measurement at the bedside. Two CRT acquisitions were made in less than 1 minute, and CRT was recorded as the average of values.

Following the procedure described by Jacquet-Lagrèze et al (22), we recorded CRT with a smartphone. We used the flashlight system to control luminosity. Two investigators (W.H., D.Z.), who were unaware of the clinical data of patients, assessed CRT with the chronometer of the software. The video was seen several times to determine the end of the CRT, CRT greater than or equal to 3 seconds was defined as abnormal (23).

Sample Size Calculation

To estimate the sample size, MFI and CRT were used as the main correlation analysis variables for calculation (16). Spearman rank correlation test was used to calculate the sample size. According to the calculation formula of PASS 15.0 software (NCSS, LLC, Kaysville, UT; https://www.ncss.com/software/pass/), we calculated the sample size was 282 patients (assumed correlation coefficient as 0.2, power = 0.90, $\alpha = 0.05$).

Statistical Analysis

Kolmogorov-Smirnov test was used for evaluation of normality of data. Data were present as median with interquartile range (IQR), means with SD, absolute numbers with percentages, when appropriate. the Mann-Whitney *U* test, the Student *t* test, the Fisher exact tests, or the chi-square test was used to compare between groups, when appropriate. Spearman rank correlation coefficients were used to assess the correlations between variables. Univariate and multivariate analyses of factors affecting an abnormal MFI or 28-day mortality were performed to identify factors independently associated with outcome. To evaluate relationship with outcome, we evaluated receiver operating characteristic curves, calculating their area, and Youden's index to identify the best cutoff value, sensitivity, and specificity. Kaplan-Meier curves and log-rank tests were used to compare differences in cumulative survival within each group.

SPSS Version 25 (IBM Corporation, Armonk, NY) and GraphPad Prism Version 9.0.1 (GraphPad Prism Software, San Diego, CA) were used for statistical analyses and preparation of figures. All the tests used were two-sided, and statistical significance was set at *p* value of less than 0.05.

RESULTS

Cohort Characteristics

A total of 346 adult ICU patients were consecutively enrolled after ICU admission. There were 64 patients who were excluded from the further analysis (39 patients were ineligible for microcirculatory assessment and 25 patients were inability to obtain high-quality SDF images). Therefore, 282 patients fulfilling the criteria were included in the final analysis. The flow diagram of this study is presented in **Supplemental Figure 1** (http://links.lww.com/CCM/H317). Microcirculatory measurements (CRT and SDF imaging) were performed at 10.2 ± 5.7 hours after ICU admission, the median recovery time (10 hr) matched the time limit (6 hr) for the completion of initial resuscitation in shock. The median interval time between laboratory index detection (lactate, blood gas) and microcirculatory assessment was 26 minutes (IQR, 9–71 min). Of 282 patients, 106 (37.6%) were female, and the median (IQR) age was 63 years (53–74 yr). Twenty-eight-day mortality rate of the whole patients observed in this cohort was 7.8% (22/282). On the first day of ICU admission, 63 patients were diagnosed with sepsis (24).

Subsequently, patients were divided into two groups based on normal (< 3 s) or abnormal (≥ 3 s) baseline CRT. In comparison with patients with a normal CRT at baseline, patients with an abnormal CRT showed a higher SOFA score (6.5 [3–9] vs 5 [2–7]; $p < 0.001$), higher APACHE II score (21 [13.75–29.25] vs 16.0 [12.0–20.0]; $p = 0.007$), higher rate of patients diagnosed with sepsis (40.7% vs 18.0%; $p < 0.001$) at ICU admission, higher lactate levels (1.70 mmol/L [1.18–3.75 mmol/L] vs 1.40 mmol/L [0.93–2.18 mmol/L]; $p = 0.008$), and higher 28-day mortality (16.7% vs 5.7%; $p = 0.016$; **Table 1**). **Supplemental Table 2** (http://links.lww.com/CCM/H317) showed the baseline characteristics of the overall study cohort.

The Relation Between CRT and Microcirculatory Flow Abnormalities

We observed a significant agreement between the CRT and microcirculatory blood flow (MFI: $r = -0.443$, $p < 0.001$; PPV: $r = -0.3708$, $p < 0.001$; HI: $r = 0.4378$, $p < 0.001$; PVD: $r = -0.1835$, $p = 0.0020$; **Fig. 1**), except TVD ($r = 0.0027$, $p = 0.9641$) and De Backer score ($r = 0.0384$, $p = 0.5202$).

We similarly observed a significant agreement between the CRT and microcirculatory blood flow in subgroups (**Supplemental Table 3**, http://links.lww.com/CCM/H317). Among 63 septic patients, CRT was related with some sublingual microcirculation parameters, including MFI ($r = -0.557$, $p < 0.001$), PPV ($r = -0.491$, $p < 0.001$), HI ($r = 0.525$, $p < 0.001$), and PVD ($r = -0.292$, $p < 0.05$). The correlation was equally valid in hypovolemic shock and septic shock.

In total cohort, spearman rank correlation coefficients between CRT and lactate (0.217, $p < 0.001$), oxygen saturation (so_2) (–0.128, $p = 0.031$), or SOFA score (0.179, $p = 0.02$) were all statistically significant. Conversely, heart rate, MAP, Pao_2, and $Paco_2$ were poorly correlated to the CRT.

Multivariable Logistic Regression Analysis for MFI Less Than 2.6

When abnormal microcirculatory flow was defined as MFI less than 2.6 (7–20), the occurrence rate of MFI abnormality on the first day of ICU admission was 21.3% (60/282). We observed CRT was longer in the patients with MFI less than 2.6 than the control group (2.50 s [1.70–4.00 s] vs 1.50 s [1.20–2.10 s]; $p < 0.001$).

In multivariable logistic regression analysis, the CRT was associated with an abnormal MFI (odds ratio [OR], 1.608; 95% CI, 2.1–10.2; $p < 0.001$) independently of the heart rate, MAP, vasopressor dose, so_2, Pao_2, $Paco_2$, lactate, and SOFA score (**Table 2**).

An area under the receiver operating characteristic curve (AUC) for abnormal microcirculatory flow was 0.782 (0.729–0.829) for CRT with a cutoff value of 1.5 seconds (sensitivity 85%, specificity 56.3%). Receiver operating characteristic curve areas for prediction of abnormal microcirculatory flow were 0.627 (0.568–0.684) for lactate, 0.594 (0.534–0.652) for SOFA score, 0.576 (0.505–0.647) for MAP, 0.579 (0.519–0.637) for Pao_2, 0.595 (0.536–0.653) for $Paco_2$, and 0.641 (0.582–0.697) for so_2.

Patients were stratified into three groups based on CRT (≤ 1.5 s group, $n = 134$; 1.5–3 s group, $n = 94$; ≥ 3 s group, $n = 54$). Microcirculatory flow abnormalities appeared to be more severe for increasing CRT (**Supplemental Fig. 2**, http://links.lww.com/CCM/H317).

TABLE 1.
Main Hemodynamic and Microcirculatory Variables of the Study Cohort Stratified by the Capillary Refill Time

Characteristic	Total Patients ($n = 282$)	CRT < 3 s ($n = 228$)	CRT ≥ 3 s ($n = 54$)	p
Age (yr)	63.0 (53.0–74.0)	63.0 (51.5–71.0)	64.0 (55.8–79.0)	0.138
Sepsis, *n* (%)	63 (22.3)	41 (18.0)	22 (40.7)	< 0.001
Sequential Organ Failure Assessment	5.0 (2.0–7.0)	4.0 (2.0–6.0)	6.5 (3.0–9.0)	0.001
Acute Physiology and Chronic Health Evaluation II	17 (12–22)	16.0 (12.0–20.0)	21 (13.75–29.25)	0.007
Vasopressors use[a], *n* (%)	123 (43.6)	83 (36.4)	40 (74.1)	< 0.001
Norepinephrine dose (μg/kg/min)	0 (0–0.07)	0 (0–0.05)	0.06 (0–0.23)	< 0.001
28-d mortality, *n* (%)	22 (7.8)	13 (5.7)	9 (16.7)	0.016
Microcirculation data				
CRT (s)	1.50 (1.20–2.33)	1.50 (1.20–1.80)	4.40 (3.30–6.98)	< 0.001
Microvascular flow index (points)	2.85 (2.63–2.95)	2.88 (2.70–2.95)	2.60 (2.06–2.85)	< 0.001
Proportion of perfused vessels (%)	98.50 (92.68–100.00)	99.10 (94.43–100.00)	91.35 (79.78–98.63)	< 0.001
Heterogeneity index	0.18 (0.07–0.41)	0.15 (0.07–0.32)	0.46 (0.17–0.70)	< 0.001
Perfused vessel density (mm/mm^2)	14.36 (12.71–15.59)	14.55 (13.22–15.79)	13.36 (10.45–15.32)	0.002
Total vessel density (mm/mm^2)	15.02 (13.60–16.34)	15.03 (13.61–16.39)	14.86 (13.37–16.34)	0.492
De Backer score	10.36 (9.60–11.36)	10.24 (9.64–11.36)	10.50 (9.44–11.52)	0.930
Macrocirculation data				
Heart rate (pulse/min)	85.91 ± 17.18	85.17 ± 16.44	89.06 ± 19.88	0.135
Temperature (°C)	36.80 (36.50–37.20)	36.80 (36.50–37.20)	37.00 (36.58–37.53)	0.053
Systolic arterial pressure (mm Hg)	129.00 (114.00–143.00)	130.00 (116.00–143.75)	126.00 (107.50–138.25)	0.107
Diastolic arterial pressure (mm Hg)	62.00 (55.00–70.00)	62.50 (55.00–70.00)	59.50 (54.75–68.25)	0.187
Mean arterial pressure (mm Hg)	82.00 (74.00–91.25)	82.50 (75.00–92.00)	82.00 (72.75–87.25)	0.223
Oxygen saturation (%)	97.25 (95.10–98.40)	97.30 (95.33–98.40)	96.70 (94.18–98.43)	0.246
Pa_{O_2} (mm Hg)	93.65 (78.10–115.00)	93.45 (79.65–115.00)	95.60 (70.58–114.50)	0.666
Pa_{CO_2} (mm Hg)	38.65 (34.30–44.45)	38.65 (34.55–43.58)	38.80 (34.18–47.35)	0.541
pH	7.42 (7.37–7.46)	7.42 (7.38–7.46)	7.40 (7.35–7.44)	0.053
Lactate (mmol/L)	1.40 (1.00–2.20)	1.40 (0.93–2.18)	1.70 (1.18–3.75)	0.008

CRT = capillary refill time.

[a]Whether patients under vasopressor support on the first day of ICU admission.

Data were presented as median (interquartile range), *n* (%), or mean ± SDS, when appropriate. p was calculated between patients (CRT < 3 s) and patients (CRT ≥ 3 s) from χ^2 test, Fisher exact test, *t* test, or Mann-Whitney *U* test, when appropriate. $p < 0.05$ was considered significant.

Based on the method described in Khanna et al (13), norepinephrine equivalent doses were calculated using the conversion factors: vasopressin (U/min × 2.5), epinephrine (μg/kg/min, × 1), phenylephrine (μg/kg/min, × 0.1), and dopamine (μg/kg/min, /150).

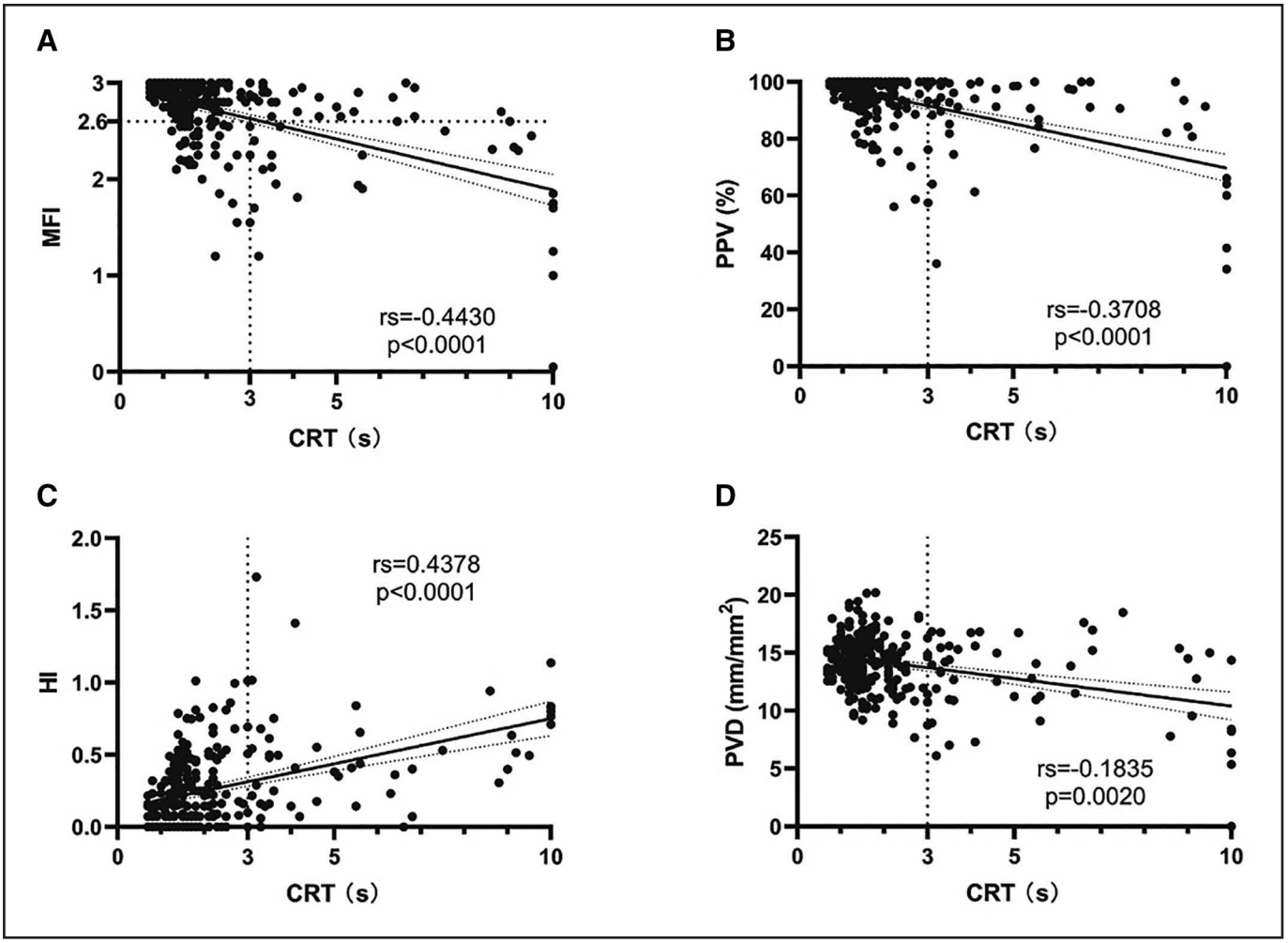

Figure 1. *Scatter plot* of capillary refill time (CRT) and sublingual microcirculatory parameters. *Scatter plots* showed the association between CRT and sublingual microcirculatory parameters. Spearman rank correlation coefficients were used. HI = heterogeneity index, MFI = microcirculatory flow index, PPV = proportion of perfused vessels, PVD = perfused vascular density.

The Relation Between CRT and Outcome

Significant increases in abnormality MFI were observed for each CRT group (≤ 1.5 s, 6.7%; 1.5–3 s, 26.6%; ≥ 3 s, 48.2%; $p < 0.001$). Similar trends were observed for 28-day mortality (≤ 1.5 s, 4.5%; 1.5–3 s, 7.4%; ≥ 3 s, 16.7%; $p < 0.001$) and the rate of sepsis (≤ 1.5 s, 17.16%; 1.5–3 s, 19.15%; ≥ 3 s, 40.7%; $p < 0.001$) (**Fig. 2*A***). In addition, a longer CRT level was accompanied by a significantly higher SOFA score and lactate level (**Fig. 2**, ***B*** and ***C***).

Sex, age, body mass index, vasopressor dose, diastolic arterial pressure, MAP, so_2, Pao_2, $Paco_2$, lactate, CRT, and SOFA score were collected at the time of microcirculation assessment. The variables mentioned above with a p value of less than 0.20 in univariable analysis for 28-day mortality were included in the multivariate model. In the multivariable logistic regression analysis, the only remaining significant predictor for 28-day mortality was CRT (OR, 1.265; 95% CI, 1.050–1.524; $p = 0.013$; **Table 3**). The AUC for CRT was 0.664 (95% CI, 0.533–0.795; $p = 0.011$; cutoff = 2.85 s; sensitivity = 50%; specificity = 82.7%). CRT not only reflected microcirculatory alterations and the severity of the disease but also contributed independently to mortality.

The AUC analysis for CRT, SOFA and sublingual microcirculation parameters (MFI, PPV, PVD, and HI) in predicting mortality were presented in **Supplemental Tables 4** and **5** (http://links.lww.com/CCM/H317). Survival analysis, by Kaplan-Meier method, confirmed a nonsignificant difference between the two groups (MFI < 2.6; CRT ≥ 3 s) for 28-day mortality (log-rank $\chi^2 = 0.005$; $p = 0.946$; **Fig. 3**). CRT is similar to MFI in defining severe clinical phenotypes and in predicting 28-day mortality.

DISCUSSION

Our observations revealed that CRT was significantly related to microcirculatory blood flow parameters (MFI,

TABLE 2.
Univariate and Multivariate Logistic Regression Analysis for Microvascular Flow Index Less Than 2.6 in Critically Ill Patients

	Univariate Analysis		Multivariate Analysis	
Parameters	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Heart rate (pulse/min)	1.016 (1.000–1.033)	0.056	1.005 (0.985–1.024)	0.638
Norepinephrine dose (μg/kg/min)	5.924 (1.611–21.778)	0.007	2.598 (0.301–22.422)	0.385
Mean arterial pressure (mm Hg)	0.986 (0.965–1.008)	0.220	0.984 (0.958–1.011)	0.247
Oxygen saturation (%)	0.969 (0.949–0.990)	0.003	0.987 (0.959–1.016)	0.374
Pao_2 (mm Hg)	0.990 (0.980–0.999)	0.030	0.988 (0.976–1.001)	0.061
$Paco_2$ (mm Hg)	1.032 (1.006–1.059)	0.017	1.002 (0.967–1.037)	0.924
Lactate (mmol/L)	1.124 (1.020–1.239)	0.018	1.036 (0.914–1.175)	0.579
Capillary refill time (s)	1.528 (1.307–1.787)	< 0.001	1.614 (1.337–1.950)	< 0.001
Sequential Organ Failure Assessment score	1.100 (1.017–1.191)	0.018	0.876 (0.756–1.016)	0.080

OR = odds ratio.

Norepinephrine equivalent doses were calculated using the conversion factors: vasopressin (U/min × 2.5), epinephrine (μg/kg/min, × 1), phenylephrine (μg/kg/min, × 0.1), and dopamine (μg/kg/min, /150).

TABLE 3.
Univariate and Multivariate Analysis of the 28-Day Mortality in Critically Ill Patients

	Univariate Analysis		Multivariate Analysis	
Parameters	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Sex (female vs male)	0.759 (0.299–1.926)	0.562		
Age (yr)	1.001 (0.974–1.029)	0.939		
Body mass index (kg/m^2)	0.955 (0.842–1.084)	0.478		
Norepinephrine dose (μg/kg/min)	15.331 (3.254–72.236)	< 0.001	7.818 (0.840–72.768)	0.071
Diastolic arterial pressure (mm Hg)	1.029 (0.996–1.063)	0.085	1.020 (0.957–1.086)	0.550
Mean arterial pressure (mm Hg)	1.027 (0.995–1.061)	0.101	1.029 (0.970–1.092)	0.345
Oxygen saturation (%)	0.976 (0.952–1.000)	0.048	0.994 (0.959–1.031)	0.759
Pao_2 (mm Hg)	1.001 (0.989–1.014)	0.839		
$Paco_2$ (mm Hg)	1.026 (0.992–1.062)	0.129	0.997 (0.955–1.042)	0.906
Lactate (mmol/L)	1.093 (0.956–1.250)	0.194	0.936 (0.759–1.155)	0.539
Capillary refill time (s)	1.364 (1.170–1.589)	< 0.001	1.265 (1.050–1.524)	0.013
Sequential Organ Failure Assessment score	1.168 (1.047–1.302)	0.005	1.092 (0.917–1.301)	0.324

OR = odds ratio.

Parameters with $p < 0.20$ after univariate analysis would be added to the multivariate model.

Norepinephrine equivalent doses were calculated using the conversion factors: vasopressin (U/min × 2.5), epinephrine (μg/kg/min, × 1), phenylephrine (μg/kg/min, × 0.1), and dopamine (μg/kg/min, /150).

PPV, and HI) in critically ill patients, and this relationship was also maintained in subgroups. Not only microcirculatory flow abnormalities (MFI < 2.6) but also 28-day mortality appeared to be more severe for increasing CRT. Similarly, increasing CRT represented more severe organ dysfunction in terms of SOFA score. In multivariable analysis, CRT was independently associated with microcirculatory flow abnormalities and 28-day mortality.

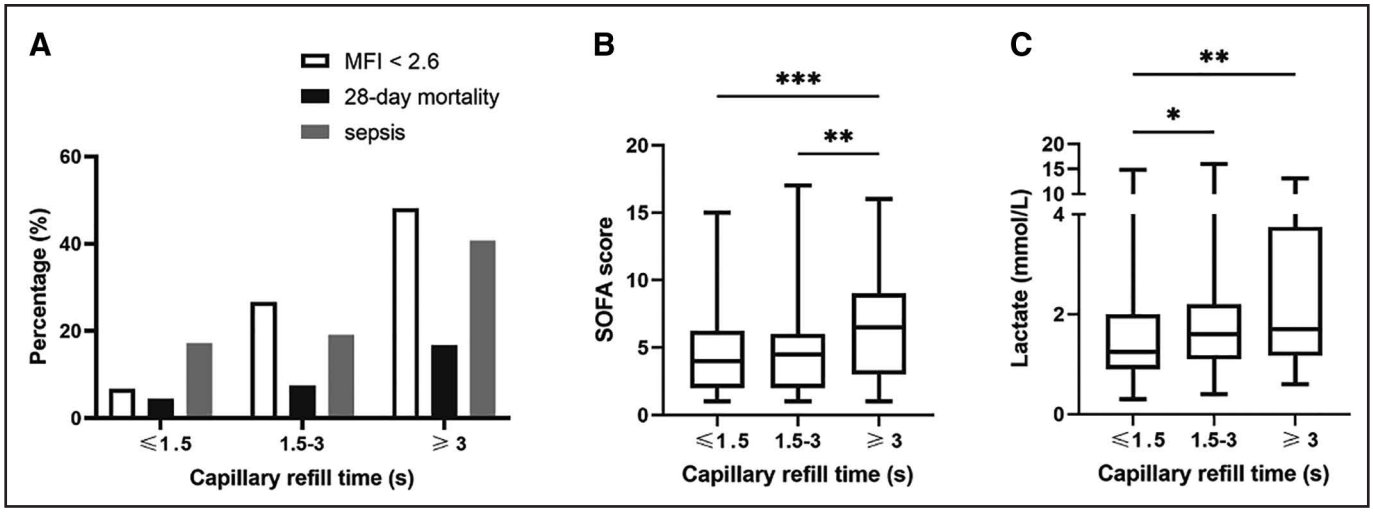

Figure 2. The relation between capillary refill time (CRT) and outcome. Patients were stratified into three groups based on CRT (≤ 1.5 s group; 1.5–3 s group; ≥ 3 s group). **A**, Distribution of abnormal microvascular flow index (MFI < 2.6), 28-d mortality, and the rate of sepsis. **B**, Sequential Organ Failure Assessment (SOFA) score per CRT group. **C**, Lactate levels per CRT group. *Boxes* represent interquartile range, *horizontal line* in the *boxes* denotes the median, and *whiskers* mean the minimum and maximum. The Mann-Whitney *U* test was used to evaluate differences between two groups. Differences were considered significant when $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. MFI = microcirculatory flow index.

Microcirculation abnormality was common in critically ill patients (25). Using the same predefined cutoff value (MFI < 2.6) (7, 26), the occurrence rate of microcirculatory derangements was 21.3% (60/282) in our observations, which was consistent with several studies (7, 27). In addition, 19.1% (54/282) of the patients displayed an abnormal baseline CRT. Abnormality microcirculation was involved in the development of organ failure and poor outcome (7, 28). Our study demonstrated that CRT can reflect the condition of peripheral perfusion in critically ill patients, with progressive increase in the CRT representing more severe risk of microcirculatory disturbances, organ dysfunction, and death.

The major new finding was that the CRT was associated with abnormal peripheral perfusion (parameters more reflected the perfusion status of microcirculation), including the adequacy of microvascular perfusion (MFI), percentage of small vessels perfused (PPV), and the heterogeneity blood flow index (HI) (29). CRT was the best predictor of the microvascular blood flow maldistribution, and it was superior to lactate, MAP and blood gas indexes (Pao_2, $Paco_2$ as well as so_2). However, there is lack of agreement between CRT and microcirculation parameters (TVD and De Backer score more reflected the overall capillary density). Brunauer et al (30) support our findings, who reported that CRT may be correlated with the pulsatility index of visceral organs in early septic shock. Raimer et al (31) reported that a normal CRT less than or equal to 2 seconds could be predictive of central venous oxygen saturation greater than or equal to 70%. Amson et al (32) reported that CRT was correlated with core-to-index finger temperature gradient in septic shock.

More patients with abnormal CRT were diagnosed with sepsis at ICU admission in our cohort. Yasufumi et al (33) supports our findings, who observed that CRT/quick SOFA (qSOFA) combination to predict sepsis in patients with suspected infection had better sensitivity than the qSOFA score alone and better specificity than the SIRS score alone. Hernandez et al (34) reported CRT status could identify different clinical phenotypes among septic shock patients. Similarly, CRT was also found that has a good ability to distinguish severe critically ill patients in our study. Our data confirm previous observations, prolonged CRT was associated with poor outcomes in terms of organ dysfunction and mortality (35, 36).

Microcirculatory alternations are observed mainly in peripheral vascular beds, including sublingual, skin, muscle, and gut. Video microscopic techniques have been used as a tool to monitor microcirculatory alterations, the effect has been widely reported (16, 37–39). Despite advances in SDF imaging, bedside assessment of microcirculation is difficult and it has not yet been incorporated into routine clinical practice. CRT is easily obtainable in the clinical setting (40). It is of great significance to determine the correlation between CRT

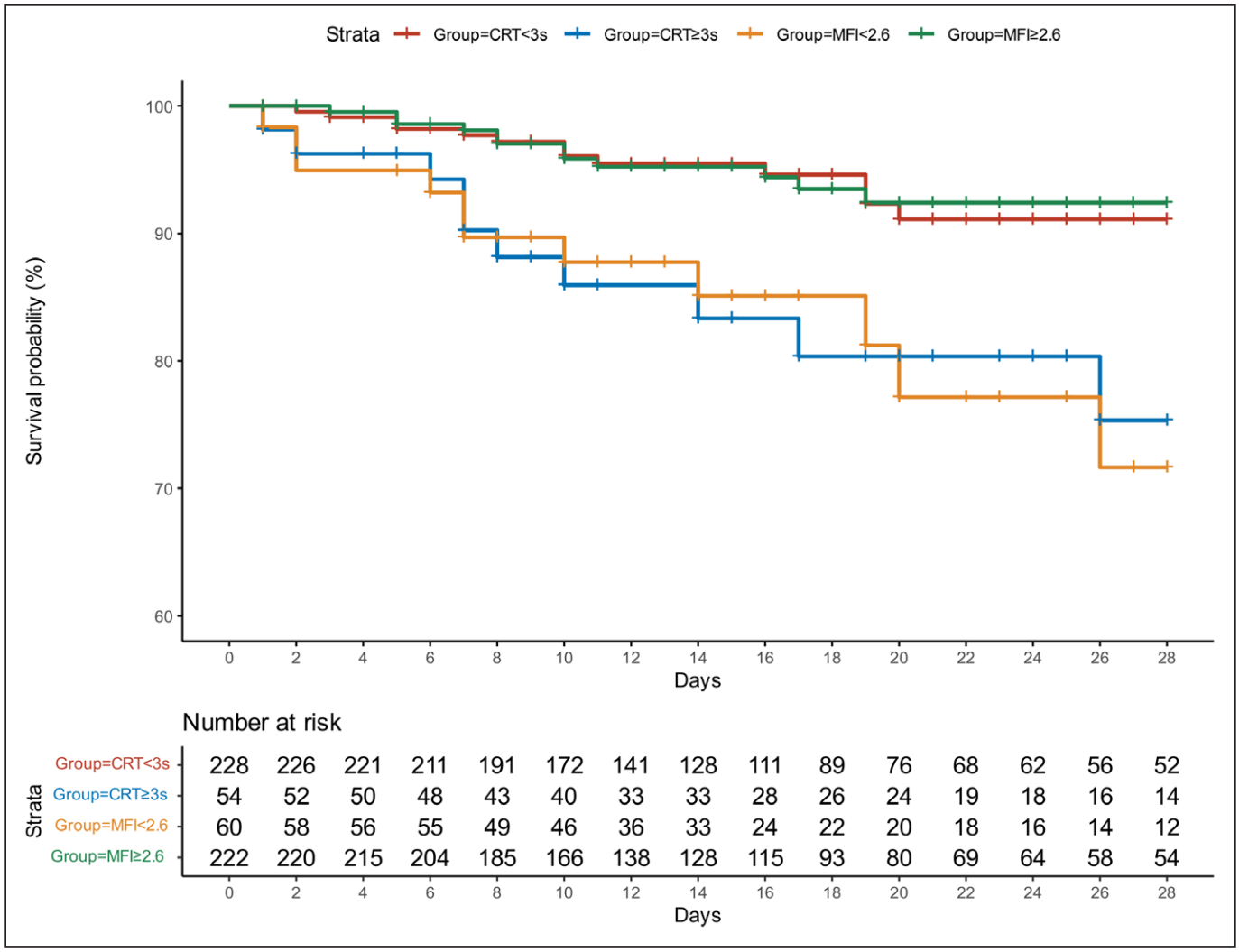

Figure 3. Kaplan-Meier analysis. Twenty-eight-d mortality was significantly different between the two groups (capillary refill time [CRT] < 3 s, CRT ≥ 3 s; log-rank $\chi^2 = 8.204$; $p = 0.004$). In the binary logistic regression analysis, an abnormal CRT at baseline was associated with 28-d mortality (odds ratio [OR], 3.308; 95% CI, 1.333–8.206; $p = 0.010$). Survival analysis confirmed a significant difference between the two groups (microcirculatory flow index [MFI] < 2.6, MFI ≥ 2.6) in terms of 28-d mortality (log-rank $\chi^2 = 10.455$, $p = 0.001$). The presence of an abnormal MFI at baseline was associated with 28-d mortality (OR, 3.500; 95% CI, 1.431–8.558; $p = 0.006$).

and SDF parameters to make clinical microcirculation monitoring simple and convenient. Similarly, CRT is not inferior to MFI in predicting 28-day mortality and defining severe clinical phenotypes in our data. CRT can be used to detect microvascular abnormalities in limited-resources regions where performing other microcirculatory assessments might be difficult. As far as we know, this is the first study specifically investigating the associations between CRT and sublingual microcirculation parameters in critically ill patients. To reduce subjective interference, a standardized CRT measurement specifies steady pressure, fixed press duration, and video recording. The video was seen several times to determine the accurate CRT.

We acknowledge some limitations of our study. First, the study was a single-point observation, and the assessments of CRT were not performed immediately after ICU admission. Single-point observation could not demonstrate that the correlation persists as patients improved or deteriorated. Resuscitation procedures, such as fluids or vasopressor doses, may influence the microcirculation. Hernandez et al (39) reported that variables exhibit very different normalization rates in septic shock survivors, sublingual microcirculatory variables exhibited the slowest recovery rate, CRT showed the fastest recovery rate. However, in multivariate logistic analysis, CRT was significantly involved with an abnormal MFI after adjusting for fluids

and vasopressor doses. Further studies need to evaluate patients immediately after ICU admission and record variable changes at different times. Second, skin temperature of the fingertip was not recorded, which may be involved with CRT. Many trials observed low ambient temperature as a strong independent factor for CRT at peripheral sites (41, 42). To avoid differences in ambient temperature may have influenced skin temperature and CRT, the ambient temperature at each patient's bedside was controlled at 22°C in the study. Third, the relationship observed between microcirculatory variables and CRT does not establish a causal association. However, CRT could indirectly reflect abnormality of microvascular flow and altered vasoreactivity, the physiologic reasoning underlying our conclusions seems logical. The observational study is exploratory and requires considerable flexibility to explore novel findings in the data (43).

CONCLUSIONS

Our study demonstrated that a baseline CRT was independently associated with abnormal microcirculation and 28-day mortality in critically ill patients (excluded patients with peripheral vascular disease), with progressive increase in the CRT representing more severe risk of microcirculatory disturbances, organ dysfunction, and mortality.

1 *Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan Hubei, China.*

2 *Clinical Research Center of Hubei Critical Care Medicine, Wuhan, Hubei, China.*

3 *Department of Critical Care Medicine, Qinghai Provincial People's Hospital, Xining, Qinghai, China.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Drs. Huang and Xiang contributed equally and share the first authorship.

Drs. Hu and Li contributed to the design of the study, interpreted the findings, and strictly revised the article. Dr. Huang performed the microcirculation measurements, analyzed the data, prepared the figures, and drafted the article. Dr. Xiang performed the offline analysis of the microcirculation parameters, interpreted the findings, and revised the article. Dr. Hu supervised the study, analyzed the data, interpreted the findings, and revised the article. Dr. Wu performed the offline analysis of the microcirculation parameters and contributed to the article. Dr. Zhang recorded the clinical and demographic data and performed the microcirculation measurements. Dr. Ma supervised the study and revised the article. All authors read and approved the final article.

This work was supported by the Chinese Medical Information and Big Data Association (No. Z-2019-1-003, to Dr. Hu), and by Translational Medicine and Interdisciplinary Research Joint Fund of Zhongnan Hospital of Wuhan University (No. ZNJC202011, to Dr. Hu), and by Qinghai Province Key R & D and Transformation Projects (No. 2019-SF-132, to Dr. Ma), and by Subject Cultivation Project of Zhongnan Hospital of Wuhan University (No. ZNXKPY2021002, to Dr. Hu).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: hubozn@whu.edu.cn; drljg5361@163.com

Consent for publication has been obtained.

The datasets for the current study are available from the corresponding author on reasonable request.

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