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Original Article

Initial 24-h perfusion index of ICU admission is associated with acute kidney injury in perioperative critically ill patients: A retrospective cohort analysis

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ABSTRACT

Background: The relationship between perfusion index (PI) and organ dysfunction in patients in the intensive care unit (ICU) is not clear. This study aimed to explore the relationship between PI and renal function in the perioperative critical care setting and evaluate the predictive efficiency of PI on patients with acute kidney injury (AKI) in the ICU.

Methods: This retrospective analysis involved 12,979 patients who had undergone an operation and were admitted to the ICU in Peking Union Medical College Hospital from January 2014 to December 2019. The distribution of average PI in the first 24 h after ICU admission and its correlation with AKI was calculated by Cox regression. Receiver operating characteristic (ROC) curves were generated to compare the ability of PI, mean arterial pressure (MAP), creatinine, blood urea nitrogen (BUN), and central venous pressure (CVP) to discriminate AKI in the first 48 h in all perioperative critically ill patients.

Results: Average PI in the first 24 h served as an independent protective factor of AKI (Odds ratio [OR]=0.786, 95% confidence interval [CI]: 0.704–0.873, P <0.0001). With a decrease in PI by one unit, the incidence of AKI increased 1.74 times. Among the variables explored for the prediction of AKI (PI, MAP, creatine, BUN, and CVP), PI yielded the highest area under the ROC curve, with a sensitivity of 64.34% and specificity of 70.14%. A cut-off value of PI ≤2.12 could be used to predict AKI according to the Youden index. Moreover, patients in the low PI group (PI ≤2.12) exhibited a marked creatine elevation at 24–48 h with a slower decrease compared with those in the high PI group (PI >2.12).

Conclusions: As a local blood flow indicator, the initial 24-h average PI for perioperative critically ill patients can predict AKI during their first 120 h in the ICU.

Introduction

Acute kidney injury (AKI) is associated with an accelerated risk of death and represents a tremendous clinical challenge for critical healthcare. It has been reported that even small elevations in creatinine in the intensive care unit (ICU) are associated with increased risk-adjusted mortality across all ICU settings.[1] In addition, AKI often accompanies the dysfunction of other organs. Clinical and epidemiological data show that AKI is associated with distant organ dysfunction in the lungs, heart, brain, and liver.[2] The mortality rate soars to 45–60% when AKI is complicated by other organ dysfunctions, such as pneumonia, acute heart failure, or sepsis.[3] Strategies to prevent even mild AKI or promote renal recovery may improve overall survival.[4] According to the pathogenesis of AKI, insufficient organ perfusion might occur before oliguria and creatinine elevation.[5] As an important blood flow indicator, blood pressure is theorized to be a risk factor for AKI. How-

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ever, blood pressure is an indirect reflection of organ blood flow. Studies have found that blood pressure is not parallel with the incidence of AKI in the ICU.[6,7] Currently, there are limited bedside, real-time monitoring indices that can reflect the worsening of renal function or be used as an early warning of AKI.

Perfusion index (PI) represents the ratio between pulsatile and non-pulsatile portions in the peripheral circulation and is predominantly affected by two main determinants: cardiac output and balance between sympathetic and parasympathetic nervous systems. Under deep sedation, it demonstrates the ability of the circulation to provide blood perfusion to tissues. Theoretically, a greater pulsatile flow means greater pulsation intensity and a greater PI value. Therefore, tissue perfusion can be reflected by PI, which acts as an ongoing monitor of local blood flow fluctuations. Studies have shown that PI <1.4 is a sign of hypoperfusion of the microcirculation, while PI <0.6 is an independent risk factor of 30-day mortality.[8,9] In recent years, evidence has accumulated a relationship between low PI and prolonged capillary refill time, and an elevated difference of extremities and core temperature, indicating that PI may reflect a deficiency of microcirculation perfusion, [10] while mottling score may indicate poor visceral organ perfusion for patients in early septic shock.[11] However, there is limited evidence directly showing a relationship between PI and organ dysfunction in patients in the ICU.[12,13]

This study focused on the relationship between PI and renal function in the perioperative critical care setting to explore the predictable efficiency of PI on AKI for patients in the ICU.

Methods

Study population

A retrospective cohort study was performed. Using the Peking Union Medical College (PUMC) Intensive Care Medical Information System and Database (PICMISD), patients who had undergone an operation and been admitted to the ICU in Peking Union Medical College Hospital (PUMCH) from January 2014 to December 2019 were identified. Exclusion criteria included: (1) patients who were younger than 18 years old and (2) patients who were admitted to the ICU for fewer than 24 h. This research was performed in accordance with the Declaration of Helsinki. The Institutional Review Board and Ethics Committee of Peking Union Medical College Hospital approved this study for human subjects (S-K1789). Written informed consent of agreement on disclosure of desensitization information for non-profit and non-interventive clinical investigation was obtained from all patients or next-of-kin before the patients were admitted to the ICU. The patient selection flowchart is shown in Figure 1.

Data collection

Philips IntelliVue monitor was used to record the basic vital signs and PI. The Philips IntelliVue monitor, mechanical ventilators, and blood gas analyzers were connected to a central server, which can achieve real-time data acquisition and synchronization. The average value of PI in each hour of the day is calculated as the PI value of the whole day. For example, the PI value of

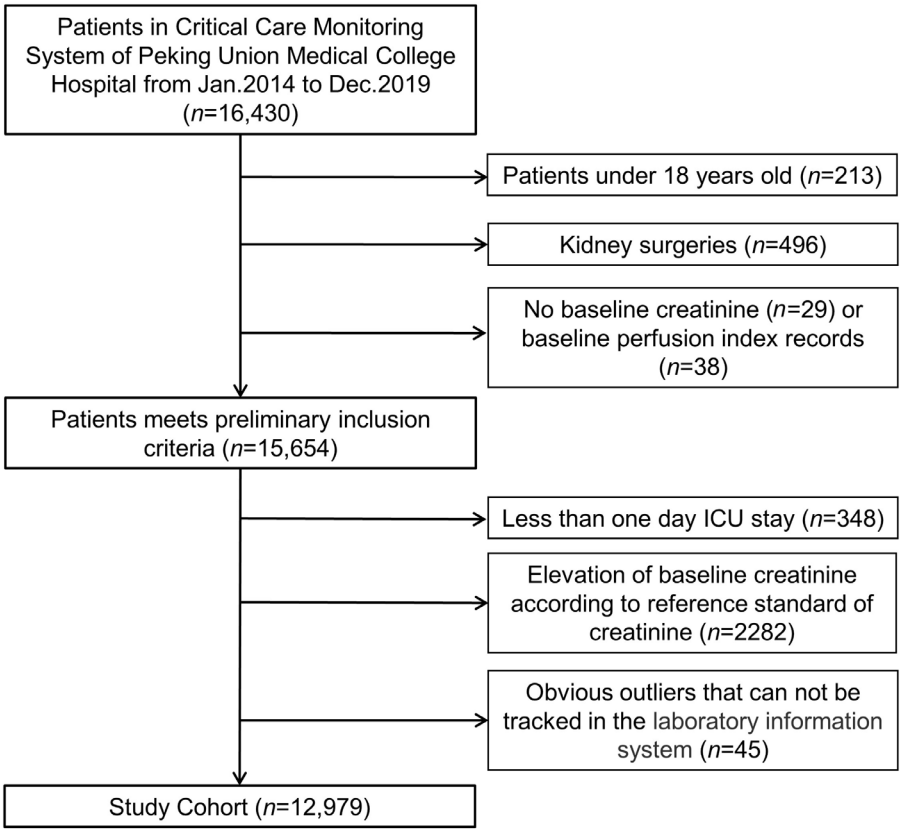


Figure 1. Flow chart depicting inclusion and exclusion criteria and patient distribution for the study. ICU: Intensive care unit.

the second 24-h period is the average PI of the 25th–48th hour after admission to the ICU. Quality control of PI includes manual checks and Philips IntelliVue algorithm checks. The clinical data of patients in this study included heart rate, respiratory rate, mean arterial pressure (MAP), body temperature, central venous pressure (CVP), PI, lactate level, data of arterial blood gas analysis, and biochemical laboratory analysis, which were all collected hourly with bedside equipment.

Study definitions

Baseline creatinine was defined as (1)The first creatinine testing value during the hospital stay (which is often obtained in the general surgical ward during pre-operative examination), if the first creatinine testing value in the ICU stay is 1.5 times higher than the first creatinine testing value during the hospital stay or the first creatinine testing value in the ICU stay increases ≥26.5 μmol/L compared with the first creatinine testing value during the hospital stay. This indicates that AKI happened before the surgery. (2)Else, the first creatinine testing value in the ICU stay (which is always obtained in the first 2 h after admission to ICU). Elevation of baseline creatinine was defined as glomerular filtration rate <90 mL/min/1.73 m^2 after adjusting for age and sex, calculated by the modified Modification of Diet in Renal Disease (MDRD) equation.

AKI was defined as any of the following: (1) increase in serum creatinine by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h; (2) increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.[14] Average creatine for 0–24 h, 24–48 h, 48–72 h, 72–96 h, and 96–120 h were extracted for the diagnosis of AKI.

Statistical analysis

Descriptive analyses were performed to compare various characteristics and the distributions of PI were also depicted as histograms. All data are presented as the mean with standard deviation for normally distributed continuous data or as the median with first quartile and third quartile otherwise. *P*-values were obtained by Welch's unequal variances *t*-test for normally distributed continuous variables or by a non-parametric test for other data. A stepwise binary logistics regression was used to evaluate possible independent risk factors for AKI within 48 h of ICU admission. Stepwise logistic regression was used for further selection. Variables with significant differences (P <0.05) in univariate analysis were enrolled in stepwise logistic regression with the mode of searching in dual directions. Minimization of the Akaike Information Criterion (AIC) was used as the criterion to optimize the optimal model. The association of mean PI for the initial 24 h in the ICU *vs*. hazard ratio (HR) of AKI outcome was performed via proportional hazard model using Cox regression. Receiver operating characteristic (ROC) curves of several indices were compared with that of mean PI for accessing the predictability of mean PI on AKI. MAP, creatinine, and blood urea nitrogen (BUN) are involved and their diagnostic ability in AKI was compared according to the area under the ROC curve (AUROC). The optimal cut-off value of mean PI was determined by the balance of specificity and sensitivity. SPSS 13.0 software package (SPSS Inc., Chicago, IL, USA) and R (version 4.0.2) with package survival were used for statistical analysis.

Decision tree algorithm

Classification decision trees based on Gini impurity were used to assess the importance of various quantities. A classifier by decision trees is represented by a tree whose leaves denote subgroups of the whole sample and each non-leaf node is labeled by a condition on one input feature. The training of a decision tree is aimed at the construction of such a tree by repeatedly splitting the sample into subgroups with certain procedures. In this study determining the occurrence of AKI, a binary tree was constructed recursively as follows.

Let $x_i(i = 1, 2, \cdots, m)$denote the $_i$ th feature and $_y$ denote the target value, $y = 1$for AKI and $_i y = 0$ for non-AKI.

Step 1: finding a best split T_1, i.e., selecting a best feature, for example, x_i and a cut-off c_1 to divide all samples into two subgroups, s_1 for $x_i \le c_1$ and S_2 for $x_i > c_1$, so as to minimize the total Gini impurity as shown in Eq. (1).

$$G(S_k) = p_1\left(1 - \sum_{j=1}^{2} p_{1j}^2\right) + p_2\left(1 - \sum_{j=1}^{2} p_{2j}^2\right) \tag{1}$$

where $p_i(i = 1, 2)$ denotes the proportion of a number of individuals in the subgroup i to the full sample and p_{ij} is the proportion of individuals belonging to the $_J$-th class in the subgroup i . It is evident that if all individuals in each subgroup belong to the same class (i.e., the individuals in a subgroup are all AKI or all non-AKI), the Gini impurity is zero.

Step 2: if the Gini impurity of S_k is zero, the class S_k is marked as a leaf node.

Step 3: if the Gini impurity of S_k is non-zero, that is, S_k contains both AKI and non-AKI cases, we return to Step 1 and further split S_k into two groups similar to Step 1 until all the subgroups have Gini impurity as zero or reach another stopping criterion such as the maximal depth of the tree, the maximal number of leaves, or the maximal number of features selected, etc.

Next, the importance of all the quantities in the predictions of AKI by decision trees was estimated. The importance score of a feature was defined as the normalized total reduction of the rate of increase in Gini impurity due to the feature. Therefore, it is necessary to define the importance scores of nodes as shown in Eq. (2).

$$I_k = \frac{N_k}{N}\left(G_k - \frac{N_{kL}}{N_k}G_{kL} - \frac{N_{kR}}{N_k}G_{kR}\right) \tag{2}$$

where N is the sample size, N_k is the number of individuals at the current node, N_{kL} is the number of individuals in the left child node, and N_{kR} is the number of individuals in the right child node.G_k is the Gini impurity at the current node. G_{kL} and G_{kR} are the Gini impurity of the left and right child node, respectively.

The importance of a feature is the summation of all the importance scores I_k of the nodes at which the child nodes (subgroups) are split owing to the given feature.

Results

Demographic and clinical characteristics of enrolled patients

During the study period (January 1st, 2014 to December 31st, 2019), a total of 12,979 patients were included in the study. The demographic and clinical characteristics of all patients involved in this study at 24 h after ICU admission are

shown in Supplementary Table 1. Among enrolled patients, 6620 (51.00%) were male and the median age was 61 years. Of the total patients, 546 (4.21%) were diagnosed with AKI during their first 120 h in the ICU and 451 patients (3.47%) died during their ICU hospitalization. Based on AKI, patients were divided into groups of AKI (n=546) and no AKI (n=12,433). As shown in Supplementary Table 2, patients with AKI were more likely to have increased heart rate, respiratory rate, CVP, lactic acid, troponin I, white blood cells, creatinine, urea, total bilirubin, albumin, activated partial thromboplastin time (APTT), prothrombin time (PT), and D-Dimer (P <0.0001 for all) and decreased oxygenation index, PI, and MAP (P <0.0001 for all). The Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment (SOFA) scores were significantly higher in the AKI group compared with those in the no AKI group (P <0.0001).

Analysis for possible risk factors of AKI

Multivariable logistic regression analysis demonstrated that PI was an independent protective factor of AKI (Odds Ratio [OR]=0.786, 95% confidence interval [CI]: 0.704–0.873, P <0.0001). Also, CVP was an independent risk factor of AKI (OR=1.235, 95% CI: 1.171–1.303, P <0.0001) and troponin I exhibited a positive correlation with AKI. Furthermore, low oxygenation index (OR=0.996, 95% CI: 0.995–0.997, P <0.0001) may contribute to the onset of AKI (Table 1).

Feature importance analysis based on decision tree algorithm for predicting AKI

A binary tree was constructed to discriminate patients who may undergo AKI (Supplementary Figure 1). The overall AUROC was 0.75. According to the feature importance analysis, the most important features were SOFA score (0.64), BUN (0.12), troponin I (0.09), PI (0.08), and MAP (0.03).

The association between PI and HR of AKI

PI had a skewed distribution with a median value of 2.58 (Figure 2). When PI decreased by one unit, the incidence of AKI increased times (95% CI: 1.61–1.88). The median of the lower quartile of PI was 1.72, which is significantly associated with higher hazard of AKI. The adjusted HR of AKI was 1.61 (95% CI: 1.51–1.72, P <0.0001), meaning that patients with a lower quartile PI of 1.72 had an estimated 61% increase in the chance of having an event at any time given that they did not have an earlier event (i.e., given that they are still in the risk set), compared with the patients with a median PI of 2.58 (Table 2). Comparing the upper quartile of 3.73 for PI to the median, the association between PI and outcome was also significant, with an estimated HR of 0.53 (95% CI: 0.48–0.58, P <0.0001).

Table 1
Binary logistics regression (stepwise) analysis for possible risk factors for AKI in the first 48 h of ICU admission.

Variable	β	S.E.	Wald	P-value	Odds ratio (95% CI)
Constant	−2.615	0.359	−7.291	<0.0001	0.073 (0.036–0.147)
CVP (mmHg)	0.211	0.027	7.753	<0.0001	1.235 (1.171–1.303)
Oxygenation index	−0.004	0.001	−7.094	<0.0001	0.996 (0.995–0.997)
PI	−0.241	0.055	−4.409	<0.0001	0.786 (0.704–0.873)
Troponin I	0.017	0.005	3.429	<0.0001	1.017 (1.007–1.027)
Direct bilirubin	0.005	0.002	2.488	0.01283	1.005 (1.001–1.009)
Blood platelet	−0.002	0.001	−2.181	0.02918	0.998 (0.997–1.000)
White blood cell	0.013	0.008	1.652	0.09855	1.013 (0.997–1.029)

AKI: Acute kidney injury; CI: Confidence interval; CVP: Central venous pressure; ICU: Intensive care unit; PI: Perfusion index; S.E.: Standard error.

Table 2
Associations between peripheral PI and AKI in the ICU.

Outcome	Level of PI (PI value)	HR (95% CI)	P-value
Time to AKI compared with median PI value (2.58)	5th percentile (0.79)	2.70 (2.35, 3.11)	2×10^{-16}
	25th percentile (1.72)	1.61 (1.51, 1.72)	
	75th percentile (3.73)	0.53 (0.48, 0.58)	
	95th percentile (5.89)	0.16 (0.12, 0.21)	

AKI: Acute kidney injury; CI: Confidence interval; HR: Hazard ratio; ICU: Intensive care unit; PI: Perfusion index.

The prognostic value of PI for AKI

ROC curves were generated to compare the ability of indicators of systemic circulation (MAP and CVP), organ perfusion (creatine and BUN), and peripheral circulation (PI) to discrim-

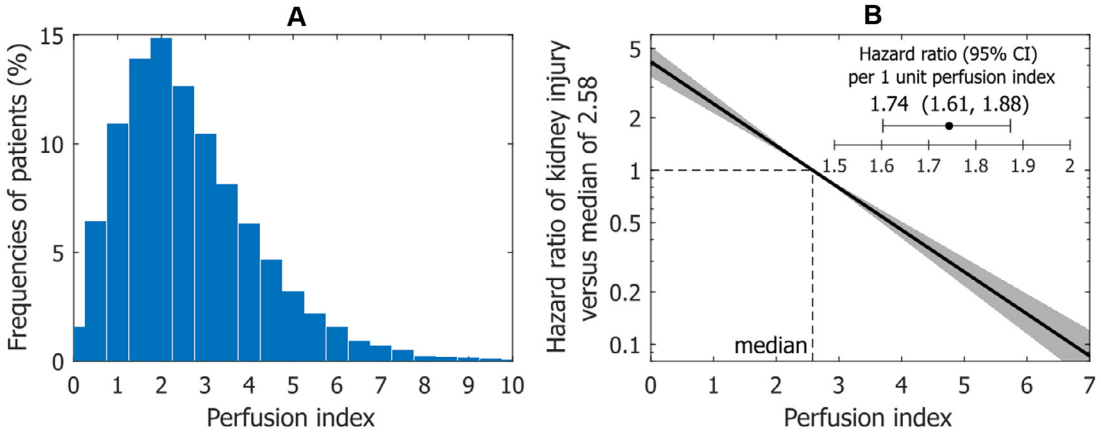
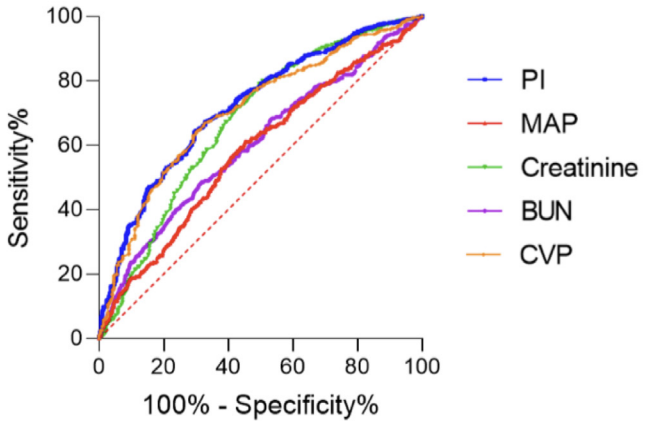


Figure 2. Distribution of average PI in the initial 24 h after ICU admission and its association with AKI. A: distribution of average PI during the first 24 h after ICU admission. B: HR of AKI compared with median average PI at 2.58 (left) and for 1.0 difference in PI (right). The solid line and shaded area indicate the estimated HR and 95% CI, respectively.
AKI: Acute kidney injury; CI: Confidence interval; HR: Hazard ratio; ICU: Intensive care unit; PI: Perfusion index.



Variable	ROC area	ROC 95% Confidence Interval	Cut-off value	Sensitivity (%)	Specificity (%)
PI	0.7194	0.6906 - 0.7483	2.115	64.34	70.14
CVP	0.7056	0.6718 - 0.7394	8.425	67.00	67.13
Creatinine	0.6724	0.6380 - 0.7069	78.71	79.01	50.35
MAP	0.5819	0.5470 - 0.6168	89.81	61.09	54.67
BUN	0.6011	0.5661 - 0.6361	5.33	48.61	68.10

Figure 3. ROC curves comparing the ability of peripheral PI, MAP, creatinine, BUN, and CVP to discriminate AKI within the first 48 h in all perioperative critically ill patients.
AKI: Acute kidney injury; BUN: Blood urea nitrogen; CVP: Central venous pressure; MAP: Mean arterial pressure; PI: Perfusion index; ROC: Receiver operating characteristic.

inate AKI within the first 48 h in perioperative critically ill patients (Figure 3). PI yielded the highest AUROC, with the sensitivity of 64.34% and the specificity of 70.14%. A cut-off value of 2.12 for PI can be used to predict AKI according to the Youden Index.

According to the cut-off value, patients were divided into two groups: the high PI group and the low PI group. Calculation of average creatine at 24–48 h, 48–72 h, and 72–96 h and comparison with average creatine for the first 24 h revealed that patients in the low PI group exhibited a marked elevation in creatine at 24–48 h and declined more slowly compared with patients in the high PI group (Supplementary Figure 2).

Discussion

This study identified an association between the average initial 24-h PI and the onset of AKI in the first 120 h of the ICU stay. As an independent risk factor for AKI, every unit decrease of the initial 24-h average PI may increase the risk of AKI by 74%. PI yielded higher AUC and specificity among CVP, creatinine, MAP, and BUN. In addition, although patients are classified as high and low PI groups simply by the initial 24-h PI, the future creatine tendency varies between the two groups. This infers that the initial 24-h PI has an advanced warning value of AKI in perioperative critically ill patients.

Blood flow is the key to organ perfusion. Traditionally, blood pressure is thought of as the impetus of blood flow, which is crucial to renal blood perfusion. However, sufficient renal blood perfusion may not be achieved only by increasing blood pressure. A reasonable explanation for this phenomenon is that “pressure” is not equivalent to “blood flow”, meaning high blood pressure fails to supply sufficient blood flow for organ and tissue perfusion. To visualize renal blood flow, the Doppler ultrasound has been proposed as a tool for the assessment of blood flow and vascular resistance. The study has demonstrated the value of the renal Doppler in assessing large arterial or venous abnormalities, and this tool has been suggested for assessing renal perfusion.[15] In the course of predicting AKI in perioperative critically ill patients, it was reported that even after the hemodynamic status has been restored to normal, renal blood flow is reduced during acute tubular necrosis as a consequence of protracted intra-renal vasoconstriction.[16] These observations have provided a deeper understanding of the relationship between renal function and blood flow. Consequently, there is an increasing demand to identify a monitoring index that may reflect renal function and blood flow.

In this study, PI was identified as a potential monitoring index that might reflect renal blood flow. PI is defined as the ratio of the pulsatile blood flow to the non-pulsatile static blood flow in a patient’s peripheral tissue (for example, fingertip).

A previous study used a cut-off of PI <1.4 as a very sensitive point for identifying abnormalities associated with vasoconstriction in critically ill patients when compared with the distribution of PI in a control group of healthy adults.[17] For microcirculation, persistent abnormalities in peripheral perfusion are associated with a poor outcome and multiple organ dysfunction, and regional tissue perfusion variables are better than global variables for predicting ICU mortality.[18–20] In our study investigating an early warning of AKI, when classified by a PI cut-off value of 2.12, patients with low PI (at initial 24 h) have significantly higher creatine elevation in the latter 72 h compared with that of patients with a high initial 24-h PI, which implies the early prognostic value of PI for AKI. Compared with PI <0.6 for discriminating patients with high 30-day mortality [21] and median PI=1.4 for healthy volunteers, [17] our warning cut-off value of PI for AKI in a perioperative critical care setting is 2.12.

These variations in cut-off values may be due to variations in adequate flow for each organ, which results in different endpoints among the different studies.

In summary, as a local blood flow indicator, PI can reflect the blood flow of the peripheral circulation to some extent. Visible PI can be treated as an equivalent sign of invisible renal blood flow, which could be used as a resuscitation goal of organ function for perioperative patients in critical care units. Furthermore, PI is a bedside parameter with characteristics of real-time updating, self-contrast comparability, and easy accessibility. Based on the above details, in order to optimize the hemodynamic management of perioperative critically ill patients, comprehensive consideration of systemic circulation and microcirculation of perioperative critically ill patients are crucial. For patients with normal mean arterial pressure and low perfusion index, we should also consider potential organ injuries or functional deficiency.

Limitations

We explore the relationship between PI and organ dysfunction in perioperative critical care patients. Nevertheless, the study must be considered in light of its limitations. First, the fluctuation of blood pressure and duration of low blood pressure may play an important role in the onset of AKI. Also, blood pressure itself may contribute to fluctuation and the absolute value of the PI. Second, there are several influencing factors that can affect PI, including body temperature, excitation of sympathetic nerves, [22] thrombus, atherosclerosis, [23] and so on. Third, limited by the definition of PI, different patients may have different baselines. Under these circumstances, a horizontal comparison may not be objective. Dynamic self-contrast monitoring should be encouraged during the study process. Finally, this study is a retrospective single-center study and a prospective multi-center study should be conducted to strengthen the findings.

Conclusions

In addition to indicators for systemic circulation and organ perfusion, the PI–which reflects peripheral perfusion—plays a more important role in predicting AKI in critically ill patients. The initial 24-h average PI for critically ill patients can predict AKI during their first 120 h in the ICU.

Ethics Statement

The ethics review board of Peking Union Medical College Hospital approved the study protocol(S-K1789). Written informed consent of agreement on disclosure of desensitization information for non-profit and non-interventive clinical investigation was obtained from all patients or next-of-kin before the patients were admitted to the intensive care unit.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2023.02.007.

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