Searching Optimal Target of Perfusion Pressure for Managing Acute Kidney Injury in Critically Ill Patients: An Analysis of Three Large Open Databases

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Abstract

Background: The optimal perfusion pressure target for acute kidney injury (AKI) in critically ill patients remains uncertain. We investigated the association between mean perfusion pressure (MPP) and AKI among critically ill patients and estimated its optimal range.

Methods: We analyzed data stored in the Medical Information Mart for Intensive Care (MIMIC) -III, eICU Collaborative Research Database (eICU-CRD), and MIMIC-IV databases. Critically ill patients receiving invasive measurements of MPP for at least 12 hours within the first 24 hours of ICU stay were included. The exposure of interest was the time-weighted average MPP (TWA-MPP) in the first 24 hours. The primary outcome was the incidence of AKI in the next 48 hours.

Results: We enrolled 7,992, 8,604, and 6,730 patients from the MIMIC-III, eICU-CRD, and MIMIC-IV databases, respectively. TWA-MPP had higher areas under the curve than mean arterial pressure in predicting AKI in the next 48 hours (0.63 vs 0.57, 0.62 vs 0.58, and 0.64 vs 0.58 in three databases, all $p < 0.001$). We observed the lowest adjusted risk of AKI when TWA-MPP above 72, 65, and 69 mmHg in the MIMIC-III, eICU-CRD, and MIMIC-IV databases, respectively. Pooled analyses indicated that per 10% increase of proportion of MPP above 65 mmHg was associated with decreased incidence of AKI (adjusted odds ratio = 0.93, 95% confidence interval = 0.92–0.94, $p < 0.001$). Furthermore, pooled analyses showed that the lowest risk of new-onset, persistence, and progression of AKI was estimated when TWA-MPP above 74, 70 and 65 mmHg, respectively.

Conclusions: MPP outperformed mean arterial pressure as a perfusion predictor of AKI. MPP of 65 mmHg or higher may be the optimal target for managing AKI in critically ill patients. The target rises to higher when reversing or preventing AKI.

Introduction

Acute kidney injury (AKI) is common in critically ill patients and is associated with poor short-term and long-term outcomes [1, 2]. It manifests in clinical and biochemical derangements characterized by a significant reduction in glomerular filtration rate (GFR)[3]. Sepsis, nephrotoxins, and hypoperfusion could contribute to the onset and progression of AKI. The mainstay of management is early intervention to address the inciting cause, with supportive care to restore kidney perfusion and oxygenation [4].

The kidney can maintain constant renal blood flow and GFR over a wide range of arterial pressures (80–180 mm Hg) with changes in vascular tone of the afferent and efferent arterioles of the glomeruli [5]. This phenomenon named autoregulation is believed to be mainly mediated by tubuloglomerular feedback and the renal myogenic response [6]. However, the autoregulation could fail in critically ill patients whose kidney is susceptible to comprised blood pressure, sepsis, and drugs interfering with neurohormonal regulation [5]. Until now, the threshold of perfusion pressure to manage AKI is not clear in critically ill patients who usually have unstable hemodynamics.

Previous studies have focused on maintaining an adequate mean arterial pressure (MAP) to manage AKI [7–12]. However, MAP is arterial inflow pressure, which fails to take venous outflow pressure into account. Central venous pressure (CVP), an indicator of the outflow pressure, is closely related to AKI in critically ill patients [13, 14]. Therefore, the mean perfusion pressure (MPP), obtained by the difference between MAP and CVP, was recently proposed to be used instead of MAP to personalize the management of tissue perfusion pressure [15, 16]. Earlier studies indicated that lower MPP or higher MPP deficits are correlated with the occurrence or progression of AKI [17–22]. Still, these studies were limited by the sample size, patients with a specific disease, and composition of different outcomes of AKI, which limited the generalization to all critically ill patients. The optimal range of MPP is still uncertain for the management of AKI, which contains preventing progression, persistence and new-onset of AKI.

Given the sparsity of evidence to support specific perfusion pressure targets in critically ill patients, we sought to describe the relationship between perfusion pressure and incidence and evolution of AKI in critically ill patients. We hypothesized that (1) MPP performs better than MAP in predicting AKI; (2) a threshold MPP may identify an optimal MPP range for the lowest risk of AKI; (3) different outcomes may have some differences in the optimal target.

Methods

Data source

All patients in the Medical Information Mart for Intensive Care (MIMIC) -III version v1.4 [23, 24], eICU Collaborative Research Database (eICU-CRD) version v2.0 [25], and MIMIC-IV version 0.4 [26] were eligible for the inclusion. MIMIC-III covers 46,476 patients out of 61,532 ICU admissions from 2001 to 2012 at the Beth Israel Deaconess Medical Center in Boston, MA, USA. The eICU-CRD covers 139,367 patients out of 200,859 ICU admissions in 2014 and 2015 in 208 U.S. hospitals. MIMIC-IV covers 50,048 patients out of 69,619 ICU admissions who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2008 and 2019. The Laboratory for Computational Physiology at the Massachusetts Institute of Technology takes charge of the maintenance of the three databases. To apply for access to the database, Dr. Wu completed the National Institutes of Health's web-based course and passed the Protecting Human Research Participants exam (record ID. 32559175). This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Study population

The inclusion criteria were (1) age 16 years or more and (2) at least 12 hours of continuous MAP and CVP invasive monitoring within the first 24 hours in the first ICU stay. Those who received dialysis, died during the first 24 hours, complicated with chronic kidney disease stage 5, or with incomplete data or low-quality MPP data were excluded.

Data extraction

We extracted all variables through Structured Query Language, including time-weighted average MPP (TWA-MPP), demographic data, baseline ICU characteristics, Charlson comorbidity index [27], admission illness severity scores [including the Sequential Organ Failure Assessment (SOFA) [28] and Oxford Acute Severity of Illness Score (OASIS) [29]], and the incidence of AKI.

Definitions

The sepsis was defined using the third sepsis definition [30, 31]. The AKI was defined using serum creatinine and urine volume according to the AKI guidelines [3], in which the baseline creatinine was estimated using a creatinine determined by back-calculation using simplified Modified Diet in Renal Disease formula assuming an estimated GFR of 75 ml/min per 1.73 m² [32]. Exposure to nephrotoxins were defined as use of vancomycin, non-steroidal anti-inflammatory drugs, amphotericin, aminoglycosides, angiotensin inhibitors or angiotensin receptor blockers and calcineurin inhibitors within 48 hours before and after ICU admission. Vasopressor dose was expressed as norepinephrine equivalents based on a recently published review of vasoactive-intropic score [33]. More detail on the study data and definition of data was presented in additional file 1.

Exposure

Since MPP is a dynamic process, TWA-MPP during the first 24 hours of ICU stay was calculated as the area under the MPP–versus–time plot as follows.

$$TWA = [(t_2 - t_1)(X_1 + X_2)/2 + (t_3 - t_2)(X_2 + X_3)/2 + \dots + (t_n - t_{n-1})(X_{n-1} + X_n)/2] / (t_n - t_1)$$

where X_n is the value of the variable of interest at the timepoint t_n .

Outcomes

The primary outcome was the incidence of AKI recognized between 24 and 72 hours following the ICU admission. Secondary outcomes included the severe AKI (defined as stage 2 or 3) and the evolution of AKI, categorized as new-onset, persistence, and progression of AKI in the same time period.

New-onset of AKI was defined as AKI identified between 24–72 hours of ICU stay in those patients without AKI recognized within the first 24 hours. In those patients with AKI recognized within the first 24 hours, the persistence of AKI was defined as the absence of reversal of AKI which meant alive and as the absence of AKI in the next 48 hours [34]; the progression of AKI was defined as dead or as the stage of AKI increase in the next 48 hours.

Statistical analysis

The categorical variables were presented as counts and percentages, including 95% confidence intervals (CI) where applicable, and continuous variables as medians and interquartile ranges (IQR). Patients were categorized into groups according to the analyzed cohort, including MIMIC-III, eICU-CRD and MIMIC-IV.

In order to determine the performance of TWA-MPP versus TWA-MAP in predicting the incidence of AKI during 24 to 72 hours of the ICU/hospital stay, we performed receiver operating characteristics area-under-the-curve (AUC) analyses using the pROC package, with 95% CI calculated by DeLong method. Then, the net reclassification index and the integrated discrimination improvement were calculated to ascertain that TWA-MPP or TWA-MAP improved the discriminatory ability when added to the base multivariate models. C-statistics and differences in the C-statistics for these multivariate models were also calculated using bootstrapping with 1000 replicates.

We built general additive models with a logit link function to plot associations between TWA-MPP and the AKI incidence. As evidence showed nonlinear relationships between TWA-MPP and outcomes, we chose the two-line piecewise linear models with a single change point to estimate change points and associations using adjusted odds ratio (AOR) and 95% confidence intervals (CI). Furthermore, we assessed the association between the AKI incidence and the proportion of MPP within the optimal interval. All the above models accounted for factors that may influence outcomes, including age, gender, BMI, ethnicity, surgical admission, cardiovascular ICU, history of hypertension, history of diabetes, history of chronic kidney disease, history of chronic heart failure, cumulative vasopressor dose, sedatives, mechanical ventilation, transfusion of RBCs, AKI at the first 24 hours, sepsis, exposure to ≥ 2 nephrotoxins, modified SOFA score (SOFA minus cardiovascular component) and OASIS score.

To assess the robustness of our findings, we conducted a secondary analysis in the vasopressor-treated population, which is the focus in the management of blood pressure. Second, we conducted a secondary analysis using median MPP as the exposure instead of TWA-MPP. Third, baseline creatinine determined by the nadir creatine during 7 days before and after ICU admission was used to confirm the association between TWA-MPP and different AKI evolutions.

To evaluate the consistency of our findings in different population that may have different optimal target, the association of TWA-MPP and the incidence of AKI were analyzed across patients who were elderly (age ≥ 65 years) with hypertension or not, with diabetes or not, with chronic kidney disease or not, with sepsis or not, with septic shock or not, with vasopressor usage or not, with higher than median SOFA score or not at the first day of ICU admission.

All analyses were performed with R version 3.6.3 software, and a two-sided $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Using the same inclusion and exclusion criteria, we included 7,992 patients admitted from 2001 to 2012 in MIMIC-III database, 8,604 patients admitted from 2014 until 2015 in eICU-CRD database, and 6,730 patients admitted from 2008 to 2019 in MIMIC-IV database (Fig. 1). The baseline characteristics of the

patients are shown in Table 1. The majority of patients in the three cohorts were male, and most patients were admitted to the cardiovascular ICU with an initial diagnosis of cardiovascular disease.

Table 1
Baseline characteristics of the study population in the first 24 hours.

	MIMIC-III (N = 7992)			eICU-CRD (N = 8604)			MIMIC-IV (N = 6730)		
Variables	Non-AKI (N = 2158)	AKI (N = 5834)	P value	Non-AKI (N = 4105)	AKI (N = 4499)	P value	Non-AKI (N = 2000)	AKI (N = 4730)	P value
Age (year)	64 (54, 73)	69 (60, 78)	< 0.001	65 (56, 73)	69 (60, 77)	< 0.001	64 (55, 72)	68 (59, 76)	< 0.001
Male (%)	1421 (65.8)	3667 (62.9)	0.015	2714 (66.1)	2760 (61.3)	< 0.001	1464 (73.2)	3177 (67.2)	< 0.001
Body mass index (kg/m ²)	26 (24, 30)	28 (25,32)	< 0.001	28 (24, 32)	29 (25, 34)	< 0.001	27 (24, 31)	29 (25, 33)	< 0.001
White race (%)	1551 (71.9)	4275 (73.3)	0.22	3240 (78.9)	3532 (78.5)	0.65	1437 (71.9)	3500 (74.0)	0.07
Surgical admission (%)	982 (45.5)	2454 (42.1)	0.006	3374 (82.2)	3201 (71.1)	< 0.001	1481 (74.1)	3300 (69.8)	< 0.001
Cardiovascular ICU (%)	1477 (68.4)	4473 (76.7)	< 0.001	2345 (57.1)	2265 (50.3)	< 0.001	1858 (92.9)	4263 (90.1)	< 0.001
History of hypertension (%)	1220 (56.5)	3702 (63.5)	< 0.001	2359 (57.5)	2803 (62.3)	< 0.001	1415 (70.8)	3608 (76.3)	< 0.001
History of diabetes (%)	455 (21.1)	1502 (25.7)	< 0.001	1101 (26.8)	1655 (36.8)	< 0.001	428 (21.4)	1052 (22.2)	0.47
History of CKD (%)	74 (3.4)	580 (9.9)	< 0.001	192 (4.7)	790 (17.6)	< 0.001	139 (6.9)	989 (20.9)	< 0.001
History of CHF (%)	436 (20.2)	1833 (31.4)	< 0.001	602 (14.7)	839 (18.6)	< 0.001	345 (17.3)	1318 (27.9)	< 0.001
Vasopressor dose (NE, mg)	0.2 (0, 2.8)	1.8 (0, 7.1)	< 0.001	0 (0, 0.4)	0.1 (0, 4.7)	< 0.001	0.5 (0, 2.5)	1.6 (0.1, 6.1)	< 0.001
Sedatives (%)	225 (10.4)	718 (12.3)	0.023	1736 (42.3)	1988 (44.2)	0.077	1602 (80.1)	3852 (81.4)	0.21
Mechanical ventilation (%)	1763 (81.7)	5195 (89.0)	< 0.001	2875 (70.0)	3545 (78.8)	< 0.001	1935 (96.8)	4588 (97.0)	0.64

AKI: acute kidney injury; CHF: chronic heart failure; CKD: chronic kidney disease; ICU: intensive care unit; MAP: mean arterial pressure; MPP: mean perfusion pressure; NE: norepinephrine equivalents; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; TWA: time weighted-average.

	MIMIC-III (N = 7992)			eICU-CRD (N = 8604)			MIMIC-IV (N = 6730)		
Transfusion of RBCs (mL)	0 (0, 0)	0 (0, 0)	< 0.001	0 (0, 0)	0 (0, 0)	0.03	0 (0, 0)	0 (0, 350)	< 0.001
Sepsis (%)	1522 (70.5)	4370 (74.9)	< 0.001	1405 (34.2)	1805 (40.1)	< 0.001	1734 (86.7)	4137 (87.5)	0.41
Exposure to ≥ 2 nephrotoxins (%)	692 (32.1)	2084 (35.7)	0.003	676 (16.5)	828 (18.4)	0.018	578 (28.9)	1416 (29.9)	0.41
AKI in the first 24 hours (%)	795 (36.8)	4447 (76.2)	< 0.001	715 (17.4)	3306 (73.5)	< 0.001	852 (42.6)	3571 (75.5)	< 0.001
Modified SOFA Score	3 (1,4)	4 (2, 5)	< 0.001	6 (4, 8)	7 (5, 9)	< 0.001	4 (2, 5)	5 (3, 6)	< 0.001
OASISs Score	30 (26, 35)	33 (28, 38)	< 0.001	28 (22, 34)	31 (25, 37)	< 0.001	32 (28, 36)	35 (30, 40)	< 0.001
TWA-MPP (mmHg)	66 (61, 71)	62 (58, 67)	< 0.001	65 (60, 71)	62 (56, 68)	< 0.001	66 (62, 71)	63 (58, 67)	< 0.001
TWA-MAP (mmHg)	75 (71, 80)	73 (69, 78)	< 0.001	75 (71, 81)	73 (68, 79)	< 0.001	75 (71, 78)	73 (69, 77)	< 0.001
AKI: acute kidney injury; CHF: chronic heart failure; CKD: chronic kidney disease; ICU: intensive care unit; MAP: mean arterial pressure; MPP: mean perfusion pressure; NE: norepinephrine equivalents; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; TWA: time weighted-average.									

The median TWA-MPP was 63.1, 63.4, and 63.8 mmHg in MIMIC-III, eICU-CRD, and MIMIC-IV, respectively (Additional file 2: Figure S1). A total of 73.0%, 52.3%, and 70.3% of the study population had recognized AKI in the 24 to 72 hours in three databases. Compared with those without AKI, the patients with AKI were more likely to be elderly, complicated more comorbidities (hypertension, diabetes, chronic kidney disease, chronic heart failure), having a higher rate of AKI in the first day, and higher severity of illness (modified SOFA score and OASIS score), and a higher probability to receive support therapy (vasopressors, mechanical ventilation, and transfusion) in three databases. The patients with AKI also had significantly higher TWA-MPP and TWA-MAP levels as compared to those without AKI. More hospital information, MPP data and outcomes are presented in Additional file 2: Table S1.

Performance of MPP vs MAP for predicting AKI

As MAP was used to represented renal perfusion pressure previously, we compared the performance of MPP versus MAP for predicting the AKI incidence in the next 48 hours (Additional file 1: Figure S2). The results consistently showed that TWA-MPP had significantly larger areas under the curve (AUCs) than

TWA-MAP for predicting the incidence of AKI (0.63 vs 0.57, 0.62 vs 0.58, 0.64 vs 0.58 in three databases, all p values < 0.001). TWA-MPP also performed better than TWA-MAP in predicting incidence of AKI using net reclassification index, integrated discrimination improvement, and C statistic (Additional file 1: Table S2) in the fully adjusted models. These findings supported that MPP was superior to MAP as a perfusion predictor of the AKI incidence.

Primary outcomes

TWA-MPP in the first 24 hours of ICU stay was associated with AKI in the next 48 hours in three databases (Fig. 2A and 2C). We observed the lowest adjusted risk of AKI when TWA-MPP was greater than 72, 65, and 69 mmHg in MIMIC-III, eICU-CRD, and MIMIC-IV, respectively (Table 2). Pooled analyses indicated that per 5 mmHg increase of TWA-MPP below the pooled change point (71 mmHg) was associated with decreased incidence of AKI (pooled AOR = 0.79, 95% CI = 0.76–0.82, p < 0.001).

Table 2

Pooled analyses of estimated change points in the association between TWA-MPP and outcomes from piecewise two-line models.

Outcomes	No. of Events/Patients	Change point (95% CI)	AOR per 5 mmHg TWA-MPP increase below the change point (95% CI)	AOR per 5 mmHg TWA-MPP increase above the change point (95% CI)
Primary Outcome				
AKI	15063/23326	71(69–73)	0.79(0.76–0.82)	1.07(1.02–1.12)
In MIMIC-III	5834/7992	72(68–75)	0.78(0.73–0.82)	1.09(1.00–1.19)
In eICU-CRD	4499/8604	65(62–68)	0.75(0.70–0.81)	1.00(0.95–1.06)
In MIMIC-IV	4730/6730	69(66–72)	0.73(0.67–0.79)	1.05(0.94–1.16)
Secondary Outcomes				
Severe AKI	9767/23326	70(68–72)	0.81(0.79–0.84)	1.08(1.03–1.14)
New-onset of AKI	3351/8213	74(70–78)	0.83(0.79–0.87)	1.08(0.98–1.18)
Persistence of AKI	10283/12266	70(68–72)	0.76(0.72–0.80)	1.12(1.04–1.22)
Progression of AKI	2949/12266	65(60–71)	0.88(0.84–0.93)	1.00(0.95–1.06)
The table shows that the lowest probability of incidence of AKI and severe AKI, new-onset, persistence, and progression of AKI was observed when TWA-MPP below a change point. The lowest of these change points was 65 mmHg. Thus, our findings support an optimal target of 65 mmHg or higher in MPP for the management of AKI. Adjusted factors included the top 19 factors listed in Table 1.				

As eICU-CRD database represented multicenter and recent practice after publishing the 2012 Kidney Disease: Improving Global Outcomes AKI guideline, and 65 mmHg was the lowest change point of MPP for the incidence of AKI in the three database, we chose MPP of 65 mmHg as a conservative perfusion pressure target for the management of AKI. We furtherly found that the increase in the proportion of MPP > 65 mmHg was associated with less incidence of AKI in unadjusted and adjusted analyses in three databases (Fig. 2B and 2D). Pooled analyses indicated that per 10% increase of proportion of MPP above 65 mmHg was associated with decreased incidence of AKI (pooled AOR = 0.93, 95% CI = 0.92–0.94, $p < 0.001$).

Secondary outcomes

TWA-MPP in the first 24 hours of ICU stay was associated with new-onset, persistence, and progression of AKI in the next 48 hours in the three databases (Fig. 3, Additional file 2: Table S3). The pooled analyses indicated that a lowest probability of new-onset, persistence, and progression of AKI were estimated when TWA-MPP above 74, 70, 65 mmHg, respectively (Table 2). Per 5 mmHg increase in TWA-MPP below these change points was associated with a lower probability of new-onset (pooled AOR = 0.84, 95% CI = 0.80–0.87, $p < 0.001$), persistence (pooled AOR = 0.76, 95% CI = 0.72–0.80, $p < 0.001$) and progression (pooled AOR = 0.88, 95% CI = 0.84–0.93, $p < 0.001$) of AKI.

Sensitivity and subgroup analyses

First, the change points of MPP were in the range of > 65 mmHg in critically ill patients who received vasopressors during the first 24 hours (Additional file 2: Figure S3, Additional file 2: Table S4). Second, the optimal target of MPP did not shift when median MPP was included into the analyses instead of TWA-MPP (Additional file 2: Figure S4, Additional file 2: Table S5). Third, the different definitions of baseline creatinine determined by the nadir creatine during 7 days before and after ICU admission did not totally affect the association between TWA-MPP and the AKI incidence (Additional file 2: Figure S5, Additional file 2: Table S6).

The association of TWA-MPP and the AKI incidence was analyzed across patients who with or without elderly (≥ 65) and hypertension, diabetes, chronic kidney disease, sepsis, vasopressor-treated, higher above median SOFA score at the first day of ICU admission (Fig. 4). The subgroup analyses consistently support the MPP of 65 mmHg or higher in the management of AKI.

Discussion

The findings of this investigation can be summarized as follows: (1) TWA-MPP in the first 24 hours of ICU stay outperformed TWA-MAP as a predictor of AKI; (2) the lowest adjusted risk of AKI was observed when TWA-MPP was 65 mmHg or higher; and (3) a lowest probability of new-onset, persistence, and progression of AKI were estimated when TWA-MPP above 74, 70, 65 mmHg, respectively.

Early in the 1950s, Semple et al. demonstrated that an increase in MAP was required to maintain the amount of blood flow through the kidneys when the renal venous pressure increased [35]. Thus, MPP may be better than MAP at reflecting renal perfusion, as the former takes the venous into account, especially in those with venous congestion named 'renal congestion'. However, comparative studies of the predictive ability of MPP versus MAP for clinical outcomes are scarce. Our data consistently supported that MPP outperformed MAP as a predictor of AKI. Our study's C-statistic was not as high as that reported by Gul et al. [20]. They reported a C-statistic of 0.81 using MPP during transcatheter aortic valve implantation to predict AKI. The low predicting ability of MPP for AKI incidence may be caused by the study population's heterogeneity and many other causes of AKI. Our results supported the hypothesis

that the MPP can replace the MAP as a clinical target in selected patients to personalize tissue perfusion pressure management.

Is there an optimal target of MPP for AKI in critically ill patients? Previous studies have focused on the MAP, which is a critical component of MPP. Heretofore, an MAP of at least 65 mmHg has been assumed to be within the zone of autoregulation for multiple organs and thus protects from organ failure in various types of shock except hemorrhagic shock [5, 36, 37]. In a multicenter randomized controlled trial on MAP targets in patients with septic shock, targeting an MAP of 80–85 mmHg did not result in significant differences in mortality compared with that with an MAP of 70–75 mmHg, but result in a lower rate of doubling of serum creatinine or receiving dialysis [7]. In addition, several recently published observational studies also favored an MAP of normal or near normal levels (75–85 mmHg) in septic shock to decrease the risk of AKI [8–10, 12]. Our study was consistent with the above studies in that the lowest risk of AKI was observed when MPP was greater than 65 mmHg, which is usually equivalent to an MAP of > 75 mmHg when CVP is approximately 10 mmHg. As compared with previous studies, one strength of our research was that the optimal target using MPP as measurement should be more precise because of MPP considering venous return and performing better than MAP as a predictor of AKI. Another advantage was that we estimated the optimal target using the predicted incidence rather than ROC analyses or groups utilized in the past [8, 10, 12], which make the optimal target of MPP clearer. The third advantage was that, with a large sample size and heterogeneity, our study had better generalization to critically ill patients. More randomized trials are necessary to prove our estimated optimal target of MPP.

The different goals for managing AKI may require a different target of MPP. In our pooled analyses, the lowest adjusted probability of new-onset, persistence, and progression of AKI was estimated when TWA-MPP above 74, 70, 65 mmHg, respectively. The change points gradually decreased when the requirement of protection for the kidney was also reduced. We proposed that the MPP of 65 mmHg or higher may be an optimal target for AKI in critically ill patients, in which 65 mmHg is also the change point for the progression of AKI, higher than previously Ostermann et al. [19] reported (60 mmHg) probably due to the large sample size. Therefore, maintaining MPP well above 65 mmHg is prudent in critically ill patients. Based on these findings, we proposed the concept frame of MPP management for AKI (Additional file 2: Figure S6), which need be confirmed in the future.

Personal hemodynamic management is proposed to achieve optimal/adequate blood flow using individual targets and adaptive multiparametric approaches [16]. Previous studies mainly focused on the MPP deficit [17, 18, 21, 22], which is defined as the difference between the basal MPP and the present MPP, indicating that an MPP goal should be achieved to decrease the MPP deficit. We proposed the optimal target of MPP was 65 mmHg or higher, which is near lower limits of normal range (about 70–95 mmHg). Our study findings were concordant with and proved those of Panwar et al. [22], who recently reported that the vasopressor-treated patients with shock are often exposed to a significant degree and duration of relative hypotension (MPP deficits), which are associated with new-onset adverse kidney-related outcomes through a prospective, multicenter observational study. Recently a large database study showed that a strategy aimed at maintaining MAP above 65 mmHg appears to be as good as one based

on the percentage reduction from baseline [38]. The question of whether MPP management should be based on an absolute MPP threshold or on a relative decline from the individual patient's baseline MPP should be investigated in the future.

Elderly patients or patients with hypertension, who usually have impaired autoregulation of blood flow to multiple organs, may benefit from a higher MPP. Our studies did not show higher change points for the incidence of AKI in elderly patients with hypertension in three databases, suggesting that the presence or absence of advanced age/hypertension may not significantly influence the target MPP. This result was in line with recent research suggesting that elderly patients do not necessarily need higher blood pressures [39, 40]. In contrast, our study only implied a higher threshold (84 mmHg) may be needed in those patients with chronic kidney disease to reduce the incidence of AKI, which suggests that blood flow in the kidney becomes pressure passive due to severe kidney injury [41].

The present analysis had some limitations. First, when considering the findings, their post hoc nature should be taken into account. Residual confusion may also influence our findings, although we tried to explain this point through adjustments of the common risk factors. Second, the data were obtained from the U.S., and therefore, the results may not be fully applied to ICUs with different practices or resources. Additionally, the current findings cannot be interpreted regarding patients who died within 24 hours of admission to the ICU or received dialysis on the first day of the ICU stay. While our findings support the optimal range of MPP for the incidence and evolution of AKI, stronger evidence, such as large randomized controlled trials, is necessary to establish causality.

Conclusions

Our analyses suggest that MPP outperformed MAP as a perfusion predictor of AKI. The estimated optimal target of MPP during the first 24 hours was 65 mmHg or higher for AKI in critically ill patients. The target of MPP may rise when needed to prevent AKI or reverse AKI. The optimal range should be verified in future randomized trials.

Abbreviations

AKI: Acute kidney injury

AOR: adjusted odds ratio

AUC: area-under-the-curve

CI: confidence intervals

CVP: central venous pressure

eICU-CRD: eICU Collaborative Research Database

GFR: glomerular filtration rate

ICU: intensive care unit

IQR: interquartile ranges

MAP: mean arterial pressure

MIMIC-III: Medical Information Mart for Intensive Care -III

MIMIC-IV: Medical Information Mart for Intensive Care -IV

MPP: mean perfusion pressure

OASIS: Oxford Acute Severity of Illness Score

SOFA: Sequential Organ Failure Assessment

TWA: time-weighted average

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the Beth Israel Deaconess Medical Center (2001–P–001699/14) and the Massachusetts Institute of Technology (No. 0403000206) approved the use of the MIMIC database. The eICU database was released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision. The re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (HIPAA Certification no. 1031219-2).

Consent for publication

Not applicable.

Availability of data and materials

Data and material of are available online; MIMIC-III at <https://mimic.physionet.org/>, eICU at <https://eicu-crd.mit.edu/>, MIMIC-IV at <https://mimic-iv.mit.edu/>. The code generated and/or analyzed during the current study are available on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BYW designed the study, conducted the data collection, data analysis, data interpretation, and wrote the manuscript. YDP and JL conducted the data collection, data analysis, and the data interpretation. CYX, KL and TL designed the study and revised the manuscript. HJM designed the study, conducted the data interpretation, and revised the manuscript. All authors reviewed and approved the version submitted for publication.

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Figures

Figure 1

Patient flow chart.

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Figure 2

The primary Outcomes. The figure demonstrates that the lowest risk of AKI was observed when time-weighted average mean perfusion pressure (TWA-MPP) greater than the change points (65 to 72 mmHg) in both unadjusted (A) and adjusted analyses (C). And the risk of AKI lowered when proportion of mean perfusion pressure > 65 mmHg increased in both unadjusted (B) and adjusted analyses (D). The above associations were fitted by general additive models with a logit link function. The adjusted models accounted for the first 19 factors listed in table 1.

Figure 2

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Figure 3

Secondary outcomes. The figure demonstrates that the lowest risk of severe AKI (A), new-onset of AKI (B), persistence of AKI (C) and progression of AKI (D) was observed when time-weighted average mean perfusion pressure (TWA-MPP) was greater than the change points (65 to 74 mmHg) in the adjusted analyses. The above associations were fitted by general additive models with a logit link function. The adjusted models accounted for the first 19 factors listed in table 1.

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Figure 4

Subgroup analyses of the estimated optimal target for AKI. The threshold of mean perfusion pressure was expressed as change points (95% CI). Each subgroup had a change point of time-weighted average mean perfusion pressure above 65 mmHg.

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