Association of Post-operative Systolic Blood Pressure Variability With Mortality After Coronary Artery Bypass Grafting

Zhuoming Zhou 1,2†, Jiantao Chen 1,2†, Guangguo Fu 1,2, Xiaodong Zhuang 2,3,4, Jian Hou 1,2, Sida Chen 1,2, Suiqing Huang 1,2, Yuan Yue 1,2, Liqun Shang 1,2, Keke Wang 5, Linhua Lv 1,2, Mengya Liang 1,2* and Zhongkai Wu 1,2*

1 Department of Cardiac Surgery, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, 2 NHC Key Laboratory of Assisted Circulation, Sun Yat-Sen University, Guangzhou, China, 3 Department of Cardiology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, 4 Center for Information Technology & Statistics, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, 5 Department of Emergency, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

Background: Blood pressure variability (BPV) has long been considered a risk factor for cardiovascular events. We aimed to investigate whether post-operative systolic BPV was associated with early and late all-cause mortality in patients undergoing coronary artery bypass grafting (CABG).

Methods: Clinical variables and blood pressure records within the first 24 h in the post-operative intensive care unit stay from 4,509 patients operated on between 2001 and 2012 were extracted from the Medical Information Mart for Intensive Care III (MIMIC-III) database. BPV was measured as the coefficient of the variability of systolic blood pressure, and we compared patients in the highest quartile with patients in the other three quartiles.

Results: After full adjustment, patients in the highest quartile of BPV were at a higher risk of intensive care unit mortality (OR = 2.02, 95% CI: 1.11–3.69), 30-day mortality (OR = 1.92, 95% CI: 1.22–3.02), and 90-day mortality (HR = 1.64, 95% CI: 1.19–2.27). For 2,892 patients with a 4-year follow-up, the association between a higher post-operative BPV and the risk of 4-year mortality was not significant (HR = 1.17, 95% CI: 0.96–1.42). The results were supported by the comparison of survival curves and remained generally consistent in the subgroup analyses and sensitivity analyses.

Conclusions: Our findings demonstrated that in patients undergoing CABG, a higher post-operative BPV was associated with a higher risk of early mortality while the association was not significant for late mortality. Post-operative BPV can support doctors in identifying patients with potential hemodynamic instability and making timely clinical decisions.

Keywords: coronary artery bypass grafting, blood pressure, variability, mortality, intensive care
INTRODUCTION

Elevated blood pressure (BP) has been demonstrated to be a dominant contributor and risk factor for a poor cardiovascular prognosis (1–3). However, BP is a dynamic physiological parameter, and the average of multiple BP readings over a period of time is insufficient to reflect the real risks of patients (4). A growing number of studies have indicated that blood pressure variability (BPV) over hours, days, and years is associated with cardiovascular events, including heart failure (5), atrial fibrillation (6), coronary artery disease, stroke, and both cardiovascular and all-cause mortality in different non-surgical populations (7–9), independent of the corresponding mean BP. The underlying mechanisms remain incompletely understood, but arterial compliance and endothelial dysfunction may be involved (10).

Coronary artery bypass grafting (CABG) is a surgical treatment for patients with severe coronary artery disease, and many of them have concomitant diseases such as hypertension, diabetes mellitus, and congestive heart failure (CHF) (11). Therefore, fluctuations of BP due to cardiac insufficiency, unsatisfactory vascular quality, and inappropriate BP management frequently occur pre- and post-operatively. Previous publications have shown that preoperative long-term BPV and intraoperative oscillation of BP can predict short-term outcomes in patients undergoing CABG (12, 13). However, it is difficult to regularly measure and control preoperative long-term BP, while post-operative BP can be routinely monitored and adjusted in the intensive care unit (ICU) after surgery.

As systolic blood pressure (SBP) has been considered to have more clinical significance than diastolic blood pressure (DBP) (14, 15), the aim of our study was to further explore the association between post-operative systolic BPV and early and late all-cause mortality in patients undergoing CABG and discuss its prognostic and therapeutic implications for optimizing post-operative BP management.

METHODS

Data Source and Study Population

Data were obtained from the Medical Information Mart for Intensive Care III (MIMIC-III) database, which is a large, freely available database with information from more than 40,000 patients who had critical care unit stays at the Beth Israel Deaconess Medical Center between 2001 and 2012 (16). Our right to access the database and acquire the data was approved by the institutional review board of the Massachusetts Institute of Technology (Cambridge, MA, USA) after one of our authors (Zhou) finished the online training for the Collaborative Institutional Training Initiative program of the National Institutes of Health (Record ID 35971811).

Among all of the patients in the MIMIC-III database, 5,007 consecutive patients undergoing CABG between 2001 and 2012 were included. The exclusion criteria were as follows: (1) missing BP measurement records (n = 274); (2) death within the first 24 h of post-operative ICU admission (n = 6); (3) length of ICU stay <24 h (n = 188); (4) BP measured <10 times within the first 24 h of post-operative ICU admission (n = 28); and (5) Patients with abnormal times (more than 1,000 times) of BP measurement (n = 2). Finally, a total of 4,509 patients were included in the study population.

Data Extraction

All data were obtained and extracted using the Structured Query Language (SQL), and pgAdmin4 for Post-greSQL was used as the administrative platform. The extracted data included: (1) demographics: age, sex, and ethnicity; (2) comorbidities defined using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, including CHF, hypertension, acute myocardial infarction (AMI), diabetes mellitus, respiratory failure, peripheral vascular disease, and end stage renal disease (ESRD); (3) concomitant surgical procedures: cardiopulmonary bypass, number of revascularized arteries, single internal thoracic artery (SITA) grafting, and concomitant valvular surgery; (4) intensive care scores: Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score II (SAPS II); (5) vital signs: SBP, DBP, heart rate, and percutaneous oxygen saturation (SpO2); (6) antihypertensive medication including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers, and diuretics; and (7) vasoactive medication including dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin.

BP Measurement and the Definition of BPV

Post-operative BP was continuously measured and recorded with a bedside BP monitor (Component Monitoring System IntelliVue MP-70; Philips Healthcare, Andover, MA) via an invasive arterial line within the first 24 h in the ICU. BP data was extracted from the database, and systolic and diastolic BPV was calculated and evaluated using the following parameters: (1) the coefficient of variation (CV) of BP, defined as the standardized deviation (SD) of SBP or DBP divided by the mean and expressed as a percentage; and (2) the SD of BP, defined as the SD of all SBP or DBP records for a patient within the first 24 h of ICU admission. Patients in the highest quartile group were defined as patients with higher BPV, and were compared with patients from the three lowest quartiles of variability.

Definition of Outcomes and Follow-Up

All patients were followed up for at least 90 days, and the primary outcome was all-cause mortality occurring within 30 days after the CABG operation. ICU and 90-day mortality were considered secondary outcomes. For the 2,892 consecutive patients who underwent surgery between 2001 and 2008, they were followed up for at least 4 years; thus, 4-year all-cause mortality was set as an additional outcome for those patients.

Statistical Analysis

The study population was categorized into two groups according to the highest and the other three CV quartiles of SBP. Continuous variables were presented as the mean ± SD and were compared by Student t-test. Categorical data were presented as numbers with proportions and were analyzed by χ²-tests.
Logistic regression models and Cox proportional hazards models were applied for the univariable and multivariable analyses to identify the association between the highest BPV quartile and mortality. Model 1 was adjusted for key demographic characteristics like age and sex; Model 2 was adjusted for age, sex, and comorbidities including CHF, hypertension, AMI, diabetes mellitus, respiratory failure, peripheral vascular disease, and ESRD. To account for the post-operative antihypertensive and vasoactive medication within the first 24 h, they were adjusted in Model 3. Model 4 was adjusted for the variables in Model 3 plus the number of BP measurements within the first 24 h. The results were presented as odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals (CIs). Survival curves at 30 days, 90 days, and 4 years were estimated using the Kaplan-Meier method and compared by the log-rank test. Subgroup analyses were performed with a logistic regression model in Model 4, according to age strata (<70 and ≥70 years), sex, CHF, hypertension, AMI, diabetes mellitus, and antihypertensive and vasoactive medication. The P for interaction was derived from a multivariable logistic regression model. Sensitivity analyses were performed by measuring BPV as SD quartiles of SBP, CV quartiles of DBP, and SD quartiles of DBP. Then, patients who were discharged or died within the first 12 h were excluded, and analyses of BPV within the first 12 h based on the remaining 4,670 patients were performed. Finally, we included patients who were discharged within 24 h or had BP measured <10 times to assess the robustness of our analysis. All tests were two-sided, and P < 0.05 were considered significant. All statistical analyses were performed using STATA, version 14.0 (StataCorp, College Station, TX).

RESULTS

Characteristics of the Patients
In total, 4,509 patients who met the selection criteria were enrolled in our study, all of whom were followed for 90 days, and among these, 2,892 patients were followed for 4 years. The baseline characteristics of the patients grouped by CV quartiles of post-operative SBP are briefly summarized in Table 1. Compared with the other three quartiles, patients in the highest BPV group were older, tend to be female, and were more likely to have CHF, diabetes mellitus and ESRD, higher BP, more BP measurements, higher intensive care scores, and less antihypertensive medication usage. The ICD-9-CM codes of the included comorbidities were summarized in Supplementary Table 1.

Systolic BPV and the Risk of ICU and 30-day Mortality
Higher ICU mortality and 30-day mortality in the highest CV quartile of SBP were found in the unadjusted and adjusted models (Models 1–4). After adjusting for age, sex, comorbidities, medications, and the number of BP measurements (Model 4), patients in the highest BPV group were still at higher risk of ICU mortality (Q4 vs. Q1–3: OR = 2.02, 95% CI: 1.11–3.69) and 30-day mortality (Q4 vs. Q1–3: OR = 1.92, 95% CI: 1.22–3.02) (Table 2).

| TABLE 1 | Baseline characteristics of patients undergoing CABG, categorized by the coefficient of variation quartiles of post-operative SBP. |
|-----------------|-----------------|-----------------|
| Variables | Coefficient of variation of SBP | P-value |
| Demographics | | |
| Age, years | 67.46 (10.89) | 70.02 (10.36) | <0.001 |
| Sex, female, n (%) | 826 (24.4) | 350 (31.1) | <0.001 |
| Ethnicity, n (%) | | |
| White | 2,377 (70.3) | 793 (70.4) | 0.256 |
| Black | 82 (2.4) | 39 (3.5) | |
| Asian | 68 (2.0) | 19 (1.7) | |
| Others | 855 (25.3) | 276 (24.5) | |
| CV of SBP | 11.59 (2.14) | 18.31 (3.15) | <0.001 |
| Comorbidities, n (%) | | |
| Congestive heart failure | 874 (25.8) | 350 (31.1) | 0.001 |
| Hypertension | 2,305 (68.2) | 773 (68.6) | 0.786 |
| Acute myocardial infarction | 267 (7.9) | 104 (9.2) | 0.158 |
| Diabetes mellitus | 1,304 (38.6) | 487 (43.2) | 0.006 |
| Respiratory failure | 136 (4.0) | 65 (5.8) | 0.014 |
| Peripheral vascular disease | 185 (5.5) | 92 (8.2) | 0.001 |
| End-stage renal disease | 121 (3.6) | 67 (5.9) | 0.001 |
| Concomitant surgical procedures | | |
| Concomitant valvular surgery, n (%) | 690 (20.4) | 251 (22.3) | 0.181 |
| Cardiopulmonary bypass, n (%) | 3,195 (94.5) | 1,045 (92.7) | 0.032 |
| SITGA grading, n (%) | 3,003 (88.8) | 969 (86.0) | 0.012 |
| Number of revascularized arteries | 2,24 (0.92) | 2,20 (0.88) | 0.196 |
| Scores | | |
| SOFA | 4.76 (2.48) | 5.37 (2.66) | <0.001 |
| SAPSII | 35.10 (11.31) | 39.61 (12.39) | <0.001 |
| Vital signs | | |
| Number of BP measurement, times | 37.15 (11.45) | 42.65 (14.40) | <0.001 |
| Mean SBP, mmHg | 112.35 (9.72) | 113.12 (9.62) | 0.020 |
| Mean DBP, mmHg | 56.90 (7.60) | 56.54 (7.02) | 0.159 |
| Heart rate, beats/minute | 85.28 (9.83) | 85.46 (9.42) | 0.593 |
| SpO2, % | 96.02 (1.23) | 98.05 (1.72) | 0.532 |
| Medication | | |
| Antihypertensive, n (%) | 2,599 (76.8) | 784 (68.6) | <0.001 |
| ACEI | 141 (4.2) | 33 (2.9) | 0.061 |
| ARB | 23 (0.7) | 10 (0.9) | 0.480 |
| Beta-blocker | 2,013 (59.5) | 534 (47.4) | <0.001 |
| CCB | 135 (4.0) | 34 (3.0) | 0.136 |
| Diuretics | 2,331 (68.9) | 714 (63.4) | 0.001 |
| Vasoactive, n (%) | 2,164 (64.0) | 723 (64.2) | 0.920 |
| Dobutamine | 68 (2.0) | 31 (2.8) | 0.142 |
| Dopamine | 71 (2.1) | 34 (3.0) | 0.077 |
| Epinephrine | 439 (13.0) | 220 (19.5) | <0.001 |
| Norepinephrine | 275 (8.1) | 128 (11.4) | 0.001 |
| Phenylephrine | 2,089 (61.8) | 691 (61.3) | 0.786 |
| Vasopressin | 135 (4.0) | 72 (6.4) | 0.001 |

The highest quartile (Q4) was compared with Q1–3. Continuous variables are presented as the mean (SD), and categorical variables are presented as numbers (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CV, coefficient of variation; DBP, diastolic blood pressure; Q, quartile; SAPS II, Simplified Acute Physiology Score II; SBP, systolic blood pressure; SITGA, single internal thoracic artery; SOFA, Sequential Organ Failure Assessment; SpO2, percutaneous oxygen saturation.
### TABLE 2 | Association between the highest quartile (Q4) vs. Q1–3 for the coefficient of variation of SBP within the first 24 h of post-operative ICU admission and mortality.

| Events | No. of events (%) | Univariable analysis | Multivariable analysis |
|--------|-------------------|----------------------|------------------------|
|        |                   | Model 1 | Model 2 | Model 3 | Model 4 |
| ICU mortality |                      |          |         |         |         |
| Q1–3   | 27 (0.80)         | 1.00 (Reference) |          |         |         |
| Q4     | 23 (2.04)         | 2.59 (1.48–4.53)   | 2.40 (1.36–4.22)      | 2.19 (1.21–3.94) | 2.02 (1.11–3.69) |
| 30-day mortality |                  |          |         |         |         |
| Q1–3   | 49 (1.45)         | 1.00 (Reference) |          |         |         |
| Q4     | 39 (3.46)         | 2.44 (1.59–3.73)   | 2.28 (1.48–3.5)       | 2.11 (1.35–3.28) | 2.07 (1.33–3.23) | 1.92 (1.22–3.02) |
| 90-day mortality |              |          |         |         |         |
| Q1–3   | 96 (2.84)         | 1.00 (Reference) |          |         |         |
| Q4     | 64 (5.68)         | 2.04 (1.48–2.79)   | 1.81 (1.32–2.49)      | 1.70 (1.24–2.34) | 1.66 (1.21–2.29) | 1.64 (1.19–2.27) |
| 4-year mortality |             |          |         |         |         |
| Q1–3   | 313 (15.03)       | 1.00 (Reference) |          |         |         |
| Q4     | 159 (19.63)       | 1.32 (1.09–1.61)   | 1.19 (0.98–1.45)      | 1.17 (0.96–1.41) | 1.16 (0.96–1.41) | 1.17 (0.96–1.42) |

Model 1 was adjusted for age and sex.
Model 2 was adjusted for age, sex, congestive heart failure, hypertension, acute myocardial infarction, diabetes mellitus, respiratory failure, peripheral vascular disease, and end-stage renal disease.
Model 3 was adjusted for the variables in Model 2 plus post-operative antihypertensive and vasoactive medication within the first 24 h.
Model 4 was adjusted for the variables in Model 3 plus the number of blood pressure measurements within the first 24 h.

ICU, intensive care unit; Q, quartile; SBP, systolic blood pressure.

### FIGURE 1 | Kaplan-Meier survival analysis among patients stratified by quartiles of the coefficient of variation of post-operative systolic BPV. Comparison of (A) 30-day, (B) 90-day, and (C) 4-year survival of the highest quartile (Q4) vs. the other three quartiles (Q1–3); Comparison of (D) 30-day, (E) 90-day, and (F) 4-year survival of the four quartiles; BPV, blood pressure variability; Q, quartile.

**Systolic BPV and the Risk of 90-day and 4-year Mortality**

The highest quartile of systolic BPV was significantly associated with a higher risk of 90-day morality in all models. The correlation remained unchanged after fully adjusting for the variables in Model 4 (Q4 vs. Q1–3: HR = 1.64, 95% CI: 1.19–2.27) (Table 2).

In the 2,892 consecutive patients who were followed up for 4 years, the univariate analysis indicated that patients with the highest systolic BPV were at higher risk of 4-year mortality.
TABLE 3 | Risk of 30-day mortality for the highest quartile (Q4) vs. Q1–3 for the coefficient of variation of SBP in different subgroups.

| Variables | Group | Number of patients | OR (95% CI) | P for interaction |
|-----------|-------|-------------------|-------------|------------------|
| Age       | <70 years | 2,325 | 2.38 (1.15–4.94) | 0.573 |
|           | ≥70 years | 2,052 | 1.73 (0.97–3.10) |        |
| Sex       | Male  | 3,333 | 2.50 (1.44–4.34) | 0.134 |
|           | Female | 1,176 | 1.07 (0.47–2.42) |        |
| CHF       | Yes   | 1,224 | 1.44 (0.78–2.69) | 0.203 |
|           | No    | 3,285 | 2.29 (1.17–4.48) |        |
| Hypertension | Yes | 3,078 | 1.76 (0.88–3.50) | 0.998 |
|           | No    | 1,431 | 2.18 (1.18–4.02) |        |
| AMI       | Yes   | 371   | 1.29 (0.40–4.18) | 0.415 |
|           | No    | 4,138 | 2.06 (1.24–3.41) |        |
| Diabetes mellitus | Yes | 1,791 | 1.25 (0.61–2.56) | 0.076 |
|           | No    | 2,718 | 2.72 (1.47–5.03) |        |
| Antihypertensive medication | Yes | 3,383 | 1.78 (0.99–3.22) | 0.787 |
|           | No    | 1,126 | 2.04 (0.97–4.30) |        |
| Vasoactive medication | Yes | 2,887 | 1.71 (1.01–2.90) | 0.466 |
|           | No    | 1,622 | 3.36 (1.30–8.68) |        |

ORs (95% CIs) were derived from a logistic regression model adjusted for age, sex, CHF, hypertension, AMI, diabetes mellitus, respiratory failure, peripheral vascular disease, end-stage renal disease, antihypertensive medication, vasoactive medication, and the number of blood pressure measurements.

DISCUSSION

To the best of our knowledge, this is the first study with a large dataset to demonstrate an association between post-operative BPV and the prognosis of patients undergoing CABG. Higher systolic BPV was associated with a higher risk of early mortality, including ICU, 30- and 90-day mortality. However, the association between higher BPV and 4-year mortality was not significant.

As early as 2010, Aronson et al. reported that intraoperative BPV was associated with 30-day mortality in patients undergoing CABG (13). Early outcomes can be predicted from intraoperative BPV, but its clinical significance is limited, as cardiopulmonary bypass and vasoactive agents are routinely used to stabilize the BP and maintain organic perfusion when the heart is not beating. In 2019, Dyke et al. analyzed 405 patients and demonstrated that preoperative 3-year visit-to-visit BPV was a risk factor for adverse outcomes after CABG (12). However, the prognostic value of preoperative visit-to-visit BPV is restricted by the inconvenience of follow-up prior to surgery, patient non-compliance, and the uncertainty of surgical timing while post-operative short-term BPV based on ICU monitoring records is a clinically applicable prognostic factor with practical clinical utility for patients undergoing CABG.

Although various studies have reported the relationship between higher BPV and the risk of cardiovascular events, the measurement, and assessment of BPV have not been standardized, and BPV could be measured in various ways, including visit-to-visit, day-to-day and beat-to-beat variability (17). Each has its strength and limits. For healthy individuals or patients with chronic diseases such as chronic kidney disease that require long-term follow-up, visit-to-visit BPV could provide additional predictive value for long-term cardiovascular events (6, 18). For patients with acute illnesses such as intracerebral hemorrhage and patients undergoing surgical treatment, short-term post-admission or post-operative BPV is easier to acquire and more appropriate to be considered as a risk factor (19, 20). In addition, BPV is commonly evaluated based on CV and SD, while the average real variability and variation independent of the mean have also been suggested (21, 22). Regardless of which approach is selected for evaluation, methodological problems, including mortality time bias, informatics censors, inappropriate adjustment, and inconsistent equipment, can inevitably lead to potential bias (23).

In our study, systolic BPV within the first post-operative 24-h was evaluated by CV, and sensitivity analyses were performed by measuring BPV as SD quartiles of SBP and CV or SD quartiles...
of DBP. In addition, logistic and Cox regression analyses based on different models and subgroup analyses were conducted, and the results of the sensitivity analyses were generally consistent, though the results based on DBP were statistically insignificant. To evaluate whether post-operative 12-h BPV was associated with the prognosis, we conducted an analysis based on the post-operative 12-h CV of SBP. Although similar trends could be observed, the results were statistically insignificant when fully adjusted. One possible explanation was that within the first 12 h, patients were in unstable conditions and primarily affected by the surgical operation and intraoperative anesthesia, analgesia, and vasoactive medication usage. In addition, volume adjustment and medical titration at the beginning of ICU admission also influences the fluctuation of BP (24). As SBP is considered to be more sensitive than DBP (14, 15) and CV can better balance the difference of baseline BP compared with SD, the first 24-h systolic BPV evaluated by CV was chosen as a more rational parameter to demonstrate the association between post-operative BPV and the prognosis in patients undergoing CABG.

Compared with 4-year mortality, the association between BPV and ICU, 30- and 90-day mortality were more replicable in the analyses, indicating that the prognostic value of BPV was more prominent for short-term outcomes. For long-term survival, although the results of the Cox regression analyses demonstrated no significant difference between the two groups, the trend still favored a higher risk in the highest quartile, and the survival curves of different quartiles were separated from each other with a P < 0.01. The insignificance was clinically reasonable since more death attributed to other unknown confounding factors occurred as time went on, and of note is that if patients could survive the initial hemodynamic instability, they were unlikely to have long-term outcome issues.

On the basis of evidence proposed by the guidelines (25), short-term 24-h BPV is considered for risk stratification in populations or cohorts while this parameter has not come into routine usage in the current clinical practice. For better observation and treatment after the CABG operation, patients are sent to the ICU where their vital signs can be monitored and recorded in the electronic health records. The evaluation of BPV supports doctors in identifying potential patients with hemodynamic instability, which might be reflective of other issues like multi-system organ dysfunction syndrome, and making timely clinical decisions based on the oscillations of BP. Although limited therapeutic strategy targeting post-operative BPV was reported, long-acting antihypertensive drugs like amlodipine and chlorthalidone were recommended to reduce long-term BPV (26, 27). However, the optimal approaches in BPV management and whether these approaches indeed bring benefits to patients, namely, an independent reduction in adverse events and mortality, need further investigations.

The current study must be interpreted within the context of its limitation. Considering most of our included patients have received medications that limit the natural variation of BP, this would be expected to bias our results toward statistical insignificance. However, analyses based on different models and parameters consistently yielded confirmatory results. Additionally, the definition of comorbidities based on the ICD-9-CM codes would be potentially not specific enough, and certain important information including preoperative risk scores, urgent or emergent surgery, intraoperative details, and cardiovascular events were not available in the database. Finally, the nature of single-center-based cohort limits the generalizability of our conclusions and further well-designed studies should be conducted to further investigate the cause-effect relationship, prognostic, and therapeutic implication of post-operative BPV.

**CONCLUSIONS**

In conclusion, our findings demonstrated that a higher systolic BPV within the first post-operative 24 h was associated with a higher risk of early mortality in patients undergoing CABG while the correlation was not significant for late mortality. Post-operative BPV can support doctors in identifying patients with potential hemodynamic instability and making timely clinical decisions.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by the Massachusetts Institute of Technology (Cambridge, MA) and the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, MA). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

**AUTHOR CONTRIBUTIONS**

ML and XZ: conception and design. ZW and LL: administrative support. ZZ, JH, and GF: provision of study materials or patients. SC, SH, YY, LS, and KW: selection and assembly of data. ZZ, JC, and ML: data analysis and interpretation. All authors contributed to the article and approved the submitted version.

**FUNDING**

This work was supported by National Natural Science Foundation of China (grant numbers 81770319, 82070297, and 81900294), Natural Science Funds of Guangdong Province (grant number 2019A1515010218), and National Key R&D Program of China (grant number 2017YFC1105000).

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.717073/full#supplementary-material
REFERENCES

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. (2002) 360:1903–13. doi:10.1016/S0140-6736(02)11911-8

2. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA. (1996) 275:1571–6. doi:10.1001/jama.1996.035502101571

3. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. (2014) 311:507–20. doi:10.1001/jama.2013.284427

4. Parati G, Ochoa JE, Salvi P, Lombardi C, Bilo G. Prognostic value of blood pressure variability and average blood pressure levels in patients with hypertension and diabetes. Diabetes Care. (2013) 36 (Suppl. 2):S312–24. doi:10.2337/dc13-2043

5. Nuyujukian DS, Koska J, Bahn G, Reaven PD, Zhou JJ. Blood pressure variability and risk of heart failure in ACCORD and the VADT. Diabetes Care. (2020) 43:1471–8. doi:10.2337/dc19-2540

6. Lee SR, Choi YJ, Choi EK, Han KD, Lee E, Cha MJ, et al. Blood pressure variability and incidence of new-onset atrial fibrillation: a nationwide population-based study. Hypertension. (2020) 75:309–15. doi:10.1161/HYPERTENSIONAHA.119.13708

7. Ernst ME, Chowdhury EK, Beilin LJ, Margolis KL, Nelson MR, Wolfe R, et al. Long-term blood pressure variability and risk of cardiovascular disease events among community-dwelling elderly. Hypertension. (2020) 76:1945–52. doi:10.1161/HYPERTENSIONAHA.120.16209

8. Mehlum MH, Liestøl K, Kjeldsen SE, Julius S, Hua TA, Rothwell PM, et al. Blood pressure variability and risk of cardiovascular events and death in patients with hypertension and different baseline risks. Eur Heart J. (2018) 39:2243–51. doi:10.1093/eurheartj/ehx760

9. Gosmanova EO, Mikkelsen MK, Molnar MZ, Lu JL, Yessayan LT, Kalantar-Zadeh K, et al. Association of systolic blood pressure variability with mortality, coronary heart disease, stroke, and renal disease. J Am Coll Cardiol. (2016) 68:1375–86. doi:10.1016/j.jacc.2016.06.054

10. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. Nat Rev Cardiol. (2013) 10:143–55. doi:10.1038/nrcardio.2013.1

11. LaPar DJ, Crosby IK, Rich JB, Quader MA, Speir AM, Kern JA, et al. Bilateral internal mammary artery use for coronary artery bypass grafting remains underutilized: a propensity-matched multi-institutional analysis. Ann Thorac Surg. (2015) 100:8–14; discussion: 5. doi:10.1016/j.athoracsur.2015.02.088

12. Dyke CM, Benz CL, Taggart CM, Klog MG, Basson MD. Systolic and diastolic blood pressure variability as risk factors for adverse events after coronary artery bypass grafting. JAMA Surg. (2019) 154:92–4. doi:10.1001/jamasurg.2018.3233

13. Aronson S, Stafford-Smith M, Phillips-Bute B, Shaw A, Gaca J, Newman M. Intraoperative systolic blood pressure variability predicts 30-day mortality in aortic coronary bypass surgery patients. Anesthesiology. (2010) 113:305–12. doi:10.1097/ALN.0b013e3181e70e9

14. Haider AW, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. Ann Int Med. (2003) 138:10–6. doi:10.7326/0003-4819-138-1-200301070-00006

15. Kannel WB, Gordon T, Schwartz MJ. Systolic versus diastolic blood pressure and risk of coronary heart disease. The Framingham study. Am J Cardiol. (1971) 27:335–46. doi:10.1016/0002-9149(71)90428-0

16. Johnson AE, Pollard TJ, Shon L, Lehman LW, Feng M, Ghassemi M, et al. MIMIC-III, a freely accessible critical care database. Sci Data. (2016) 3:160035. doi:10.1038/sdata.2016.35

17. Webb AJ, Lawson A, Wartolowska K, Mazzucco S, Rothwell PM. Progression of beat-to-beat blood pressure variability despite best medical management. Hypertension. (2021) 77:193–201. doi:10.1161/HYPERTENSIONAHA.120.16290

18. Gregg LP, Hedayati SS, Yang H, Van Buren PN, Banerjee S, Naveenethan SD, et al. Association of blood pressure variability and diuretics with cardiovascular events in patients with chronic kidney disease stages 1–5. Hypertension. (2021) 77:948–59. doi:10.1161/HYPERTENSIONAHA.120.16117

19. de Havenon A, Majersik JJ, Stoddard G, Wong KH, McNally JS, Smith AG, et al. Increased blood pressure variability contributes to worse outcome after intracerebral hemorrhage. Stroke. (2018) 49:1981–4. doi:10.1161/STROKEAHA.118.022133

20. Divani AA, Liu X, Di Napoli M, Lattanzi S, Zai W, James ML, et al. Blood pressure variability predicts poor in-hospital outcome in spontaneous intracerebral hemorrhage. Stroke. (2019) 50:2023–9. doi:10.1161/STROKEAHA.119.025514

21. Mena L, Pintos S, Queipo NV, Azpiruoa JA, Maestre G, Sulbarán T. A reliable index for the prognostic significance of blood pressure variability. J Hypertens. (2005) 23:505–11. doi:10.1097/01.jhh.0000160205.81652.5a

22. Yano Y. Visit-to-visit blood pressure variability—what is the current challenge? Am J Hypertens. (2017) 30:112–4. doi:10.1093/ajh/hwp124

23. Stevens SL, Wood S, Koshiaris C, Law K, Glassiou P, Stevens RJ, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ. (2016) 354:i4098. doi:10.1136/bmj.i4098

24. Costa AS, Costa PH, de Lima CE, Pádua LE, Campos LA, Baltatu OC. ICU blood pressure variability may predict nadir of respiratory depression after coronary artery bypass surgery. Front Neurosci. (2015) 9:506. doi:10.3389/fnnins.2015.00506

25. Schutte R, Thijs L, Liu YP, Asayama K, Jin Y, Oddli A, et al. Within-subject blood pressure level–not variability–predicts fatal and nonfatal outcomes in a general population. Hypertension. (2012) 60:47–54. doi:10.1161/HYPERTENSIONAHA.112.202143

26. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet. (2010) 375:906–15. doi:10.1016/S0140-6736(10)60235-8

27. Kollas A, Stergiou GS, Kyriakoulis KG, Bilo G, Parati G. Treating prognosis: is amlopidine the drug of choice? Hypertension. (2017) 70:862–6. doi:10.1161/HYPERTENSIONAHA.117.10887

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Zhou, Chen, Fu, Zhuang, Hou, Chen, Huang, Yue, Shang, Wang, Lv, Liang and Wu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.