Association of latent class analysis-derived subphenotypes of acute kidney injury with mortality in critically ill patients with cardiovascular disease: a retrospective cohort study

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Abstract

Background: To explore the potential heterogeneity of acute kidney injury (AKI) and evaluate the prognostic differences among AKI subphenotypes in critically ill patients with cardiovascular diseases.

Methods: Data were extracted from the Medical Information Mart for Intensive Care (MIMIC)-III database. Latent class analysis (LCA) was used to explore the potential subphenotypes of AKI in critically ill patients with cardiovascular diseases. The number of classes was identified by the Bayesian information criterion and entropy. The differences in prognostic ability among the AKI subphenotypes were evaluated by logistic regression analysis.

Result: A total of 7738 AKI patients were enrolled in this study. Using LCA, AKI patients were divided into 4 heterogeneous subphenotypes, which were obviously different from the Kidney Disease: Improving Global Outcomes (KDIGO) stages. Interestingly, class 3 classified by LCA was dominated by stage 2, while the mortality rate in class 3 was significantly different from that in class 1 (15.2% vs. 1.6%, \( p < 0.05 \)). After further adjustment, the mortality rate in class 3 remained higher than that in class 1, with an odds ratio of 12.31 (95% confidence interval, 8.96–16.89).

Conclusions: LCA was feasible for AKI classification in critically ill patients with cardiovascular disease, and 4 distinct subphenotypes of AKI patients with different prognoses were identified. Our results highlighted the potential heterogeneity of AKI patients, which is worthy of further investigation.

Keywords: Acute kidney injury, Subphenotypes, Latent class analysis, Mortality, Cardiovascular disease

Introduction

Acute kidney injury (AKI) is a serious clinical event characterized by a sudden decline in renal function, with a 3.2–78% incidence in admission to the intensive care unit (ICU) [1] and a significant correlation with mortality [2]. There is potential heterogeneity in AKI, which leads to complex clinical manifestations and few effective treatments [3]. AKI is also common among patients with cardiovascular disease and is associated with higher
mortality in these patients [4, 5]. However, the types of comorbidities and pathophysiological changes in patients with cardiovascular disease were significantly different from those in ICU patients, leading to further heterogeneity of AKI in patients with cardiovascular disease [5, 6]. Whether the prognoses among AKI patients with different clinical features vary remains unknown.

Latent class analysis (LCA), a popular method based on multidimensional data, is used to identify potential heterogeneity among individuals. Emerging studies using LCA to identify the subphenotypes of patients with a single disease, such as metabolic syndrome [7] and obstructive sleep apnea [8], have recently been reported. In the ICU, 2 AKI subphenotypes were identified by LCA, which present different risks for adverse clinical outcomes [9]. However, there is currently no study on the classification of AKI in critically ill patients with cardiovascular disease, and it is unclear whether LCA is applicable to the subphenotype exploration in this group of patients.

In this study, data were obtained from the Medical Information Mart for Intensive Care (MIMIC)-III database, which is composed of a large amount of clinical and test data collected from the ICU [10]. We aimed to evaluate the feasibility of LCA for exploration of AKI subphenotypes in critically ill patients with cardiovascular disease and compare the prognosis among these AKI subphenotypes to provide a theoretical basis for clinical differentiation and prognosis prediction of distinct AKI subphenotypes.

Methods
Data source
Related data were extracted from the MIMIC-III database established by Beth Israel Deaconess Medical Center in Boston, Massachusetts, USA [10]. The database includes information on clinical diagnoses and treatments for more than 30,000 patients in the ICU, collected between 2001 and 2012. Information collected in the database includes patient demographics, vital signs, laboratory test results, procedures, medical treatment, clinical records, imaging reports, and patient death events. The use of the MIMIC-III database was approved by the review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.

Study population
Adult patients with a length of ICU stay longer than 1 day were included. For patients who were recorded with multiple admissions, only the first ICU admission was extracted. In this study, we focused on patients with cardiovascular disease in the cardiac surgery recovery unit (CSRU) or cardiac care unit (CCU). AKI within 48 h and AKI stage were diagnosed based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [11]. Eventually, 7738 AKI patients in the CSRU or CCU were enrolled for the following analysis (Fig. 1).

Covariates and outcomes
Baseline characteristics were extracted within the initial 24 h after CSRU or CCU admission. The covariates included in this study were as follows: age, sex, body mass index (BMI), unit type, heart rate, respiratory rate, oxygen saturation (SpO2), temperature, glucose, systolic blood pressure, diastolic blood pressure, 24-h urine output, use of ventilation, and administration of vasopressors, sedatives, and furosemide.

Comorbidities included coronary artery disease (CAD), atrial fibrillation, congestive heart failure (CHF), hypertension, stroke, sepsis, diabetes, chronic obstructive pulmonary disease (COPD), renal disease, liver disease, and malignancy, which were recorded as International Classification of Diseases, Ninth Revision (ICD-9) codes. Procedures included cardiopulmonary bypass, coronary artery bypass grafting (CABG), and left heart catheterization.

Laboratory test measurements included white blood cell count and levels of hemoglobin, platelets, chloride, sodium, potassium, blood urea nitrogen (BUN), bicarbonate, and creatinine.

Severity at admission was measured by the Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score II (SAPS II) score, Elixhauser comorbidity score, and length of ICU stay. The outcome of the current study was 28-day mortality, which was also extracted from the database.
LCA
LCA was used to explore the potential subphenotype of AKI patients. In this study, baseline characteristics, comorbidities, procedures, and laboratory test measurements, which were described above, were brought into LCA algorithm. The Bayesian information criterion (BIC) criterion, Vuong–Lo–Mendell–Rubin test, and entropy were enrolled to evaluate the proper number of classes. The BIC was a criterion for class number selection, with lower values suggesting model parsimony. Vuong–Lo–Mendell–Rubin test was used to evaluate whether the number of classes provided improved model fit compared to a model using one fewer class. Entropy, an index of how well the classes were separated, ranged from 0 to 1, and values > 0.8 were generally considered a sign of a useful model. LCA was carried out using Mplus software (version 8.5, Muthen & Muthen, Los Angeles, USA).

Statistics analyses
Continuous variables are presented as the SEM ± SD or median (interquartile range), as appropriate. Categorical variables are presented as numbers (percentages). The chi-square test of categorical variables and analysis of variance or the Kruskal–Wallis test of continuous variables were used for comparisons among groups. In multivariable logistic regression, model 1 was adjusted for age, BMI, and male sex. Model 2 was adjusted for model 1 plus AKI stage. Model 3 was adjusted for Model 2 plus SAPS II score, SOFA score, and Elixhauser comorbidity score. The odds ratio (OR) and 95% confidence interval (CI) values were determined by logistic regression for the prognosis of different classes. Principal component analysis were used to graphically show heterogeneity across AKI classes. DeLong test was used to compare the area under the receiver operating characteristic curve (AUC) values of models. A two-tailed \( p \) value < 0.05 was considered statistically significant in our study. Statistical analyses were carried out using SPSS (version 23.0, IBM, New York, USA) and the R tool (version 6.3, R Foundation for Statistical Computing, Vienna, Austria).

Results
Identification of AKI subphenotypes
The model with 4 classes showed a significantly better model fit than the model with 3 classes (\( p < 0.001 \)), while the model with 5 classes showed no significantly better model fit than the model with 4 classes (\( p = 0.398 \)). The entropy of all models was larger than 0.8, which was the threshold of the useful model. Thus, 4 classes were selected for further analyses (Fig. 2). Then, each patient was assigned to the most likely class by LCA.

Baseline characteristics of AKI subphenotypes
There were significant differences in baseline characteristics among the 4 classes (all \( p < 0.05 \)) (Table 1). Principal component analysis showed that class 4 and 3 were distributed away from class 1 and class 2 (Fig. 3). Both class 1 and class 2 were dominated by CSRU patients, and class 1 was more likely to be male (74.1%) and have CAD (99.4%). Patients in class 2 were the youngest (64.24 ± 14.23 years) and least likely to have diabetes (14.1%), CABG (0.1%), and left heart catheterization (12.6%). Class 4 was dominated by hypertension (52.2%), renal disease (52.5%), and CHF (66.2%), which was characterized by the highest creatinine level and the lowest urine output. Compared with the other 3 classes, class 3 had the highest diastolic blood pressure and the lowest use rate of ventilation (33.0%), vasopressors (26.3%), and sedatives (28.0%).

Comparison of AKI stages and disease severity among the 4 AKI classes
The distribution of AKI stages differed among the 4 AKI classes. The majority of patients in class 1, class 2, and class 3 were stage 2 patients. Class 4 was dominated by stage 3 patients (53.1%) (Table 2). The SAPS II score, SOFA score, and Elixhauser score were highest in class 4 (\( p < 0.001 \)) (Table 3).

Differences in prognosis among the 4 AKI classes
Patients in class 4 had the highest 28-day mortality rate (25.1%), followed by those in class 3 (15.2%). Additionally, the length of ICU stay was the longest in class 4 (\( p < 0.001 \)) (Table 3). In univariate model, class 4 showed...
| Variables                              | Class 1                          | Class 2                          | Class 3                           | Class 4                          | p      |
|---------------------------------------|----------------------------------|----------------------------------|-----------------------------------|----------------------------------|--------|
| Number                                | 3321                             | 1401                             | 2466                              | 550                              | <0.001 |
| Age, years                            | 68.67 ± 10.54                    | 64.24 ± 14.23                    | 68.68 ± 13.72                     | 70.50 ± 12.59                    | <0.001 |
| Male                                  | 2462 (74.1)                      | 742 (53.0)                       | 1394 (56.5)                       | 354 (64.4)                       | <0.001 |
| Body mass index, kg/m²                | 29.46 ± 5.93                     | 28.75 ± 6.67                     | 29.18 ± 7.41                      | 30.47 ± 8.12                     | <0.001 |
| CSRU                                  | 3198 (96.3)                      | 1368 (97.6)                      | 523 (21.2)                        | 147 (26.7)                       | <0.001 |
| Heart rate, /min                      | 85.63 ± 8.95                     | 83.84 ± 10.98                    | 82.54 ± 16.39                     | 80.29 ± 15.77                    | <0.001 |
| Respiratory rate, /min                | 16.95 ± 2.68                     | 16.95 ± 2.94                     | 19.31 ± 3.80                      | 19.10 ± 3.89                     | <0.001 |
| SpO₂ %                                | 98.04 ± 1.39                     | 98.01 ± 1.33                     | 97.84 ± 2.23                      | 97.03 ± 2.77                     | <0.001 |
| Temperature, °C                       | 36.87 ± 0.47                     | 36.85 ± 0.55                     | 36.81 ± 0.67                      | 36.60 ± 0.69                     | <0.001 |
| Glucose, mg/dL                        | 132.63 ± 21.00                   | 128.59 ± 20.67                   | 148.59 ± 47.06                    | 149.27 ± 50.64                   | <0.001 |
| Systolic blood pressure, mmHg         | 112.09 ± 8.64                    | 111.97 ± 9.54                    | 115.95 ± 16.45                    | 114.78 ± 17.71                   | <0.001 |
| Diastolic blood pressure, mmHg        | 56.02 ± 6.04                     | 57.54 ± 6.92                     | 60.46 ± 10.57                     | 55.45 ± 11.01                    | <0.001 |
| Urine output, mL                      | 1945.00 (1458.50–2636.00)        | 1840.00 (1305.00–2627.50)        | 1559.00 (996.75–2404.25)          | 835.50 (247.25–1589.75)          | <0.001 |
| Ventilation                           | 3285 (98.9)                      | 1386 (98.9)                      | 814 (33.0)                        | 268 (48.7)                       | <0.001 |
| Vasopressor                           | 2906 (87.5)                      | 1065 (76.0)                      | 648 (26.3)                        | 265 (48.2)                       | <0.001 |
| Sedative                              | 3204 (96.5)                      | 1367 (97.6)                      | 691 (28.0)                        | 226 (41.1)                       | <0.001 |
| Furosemide                            | 566 (17.0)                       | 292 (20.8)                       | 228 (9.2)                         | 82 (14.9)                        | <0.001 |
| CAD                                    | 3302 (99.4)                      | 69 (4.9)                         | 1282 (52.0)                       | 253 (46.0)                       | <0.001 |
| Atrial fibrillation                    | 1428 (43.0)                      | 658 (47.0)                       | 866 (35.1)                        | 231 (42.0)                       | <0.001 |
| CHF                                    | 817 (24.6)                       | 384 (27.4)                       | 1226 (49.7)                       | 364 (66.2)                       | <0.001 |
| Hypertension                           | 264 (7.9)                        | 51 (3.6)                         | 220 (8.9)                         | 287 (52.2)                       | <0.001 |
| Stroke                                 | 207 (6.2)                        | 75 (5.4)                         | 197 (8.0)                         | 27 (4.9)                         | 0.002  |
| Sepsis                                 | 278 (8.4)                        | 218 (15.6)                       | 731 (29.6)                        | 293 (53.3)                       | <0.001 |
| Diabetes                               | 1326 (39.9)                      | 197 (14.1)                       | 739 (30.0)                        | 289 (52.5)                       | <0.001 |
| COPD                                   | 317 (9.5)                        | 137 (9.8)                        | 406 (16.5)                        | 91 (16.5)                        | <0.001 |
| Renal disease                          | 270 (8.1)                        | 52 (3.7)                         | 248 (10.1)                        | 289 (52.5)                       | <0.001 |
| Liver disease                          | 32 (1.0)                         | 27 (1.9)                         | 56 (2.3)                          | 31 (5.6)                         | <0.001 |
| Malignancy                             | 124 (3.7)                        | 115 (8.2)                        | 287 (11.6)                        | 48 (8.7)                         | <0.001 |
| Cardiopulmonary bypass                | 3150 (94.9)                      | 1089 (77.7)                      | 267 (10.8)                        | 77 (14.0)                        | <0.001 |
| CABG                                   | 3164 (95.3)                      | 2 (0.1)                          | 242 (9.8)                         | 62 (11.3)                        | <0.001 |
| Left heart catheterization            | 1435 (43.2)                      | 177 (12.6)                       | 1143 (46.4)                       | 146 (26.5)                       | <0.001 |
| White blood cell count, × 10⁹/L        | 13.16 ± 5.15                     | 13.08 ± 6.19                     | 12.27 ± 6.03                      | 12.78 ± 7.30                     | <0.001 |
| Hemoglobin, g/dL                      | 9.84 ± 2.04                      | 9.93 ± 1.93                      | 11.72 ± 1.99                      | 10.03 ± 1.63                     | <0.001 |
| Platelet, × 10⁹/L                     | 164.38 ± 60.03                   | 161.50 ± 67.91                   | 239.12 ± 101.52                   | 219.03 ± 100.62                  | <0.001 |
| Chlordex, mg/dL                       | 108.09 ± 3.96                    | 108.65 ± 4.16                    | 103.54 ± 5.16                     | 101.58 ± 6.78                    | <0.001 |
| Sodium, mg/dL                         | 136.47 ± 2.78                    | 137.52 ± 3.36                    | 138.19 ± 4.23                     | 136.30 ± 5.40                    | <0.001 |
| Potassium, mg/dL                      | 4.55 ± 0.82                      | 4.34 ± 0.82                      | 4.10 ± 0.65                       | 4.69 ± 0.87                      | <0.001 |
| BUN, mg/dL                             | 17.49 ± 7.50                     | 16.53 ± 7.00                     | 23.20 ± 10.99                     | 68.05 ± 23.68                    | <0.001 |
| Bicarbonate, mg/dL                    | 23.60 ± 2.39                     | 23.36 ± 2.81                     | 24.49 ± 4.61                      | 22.00 ± 5.33                     | <0.001 |
| Creatinine, mg/dL                     | 0.80 (0.70–1.00)                 | 0.80 (0.60–1.00)                 | 1.00 (0.80–1.40)                  | 3.30 (2.50–5.10)                 | <0.001 |

Continuous variables are presented as the SEM ± SD or median (interquartile range), as appropriate. Categorical variables are presented as numbers (percentages).

The chi-square test of categorical variables and analysis of variance or Kruskal–Wallis test of continuous variables were used for comparisons among groups. AKI, acute kidney injury; LCA, latent class analysis; CSRU, cardiac surgery recovery unit; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; BUN, blood urea nitrogen.
the highest risk of 28-day death with an OR of 21.06 (95% CI 15.06–29.44) (Additional file 1: Table S1). After adjustment in model 3, class 3 showed the highest risk of 28-day death with an OR of 16.21 (95% CI 11.83–22.18), followed by class 4 with an OR of 8.31 (95% CI 5.75–12.02) (Table 4).

**Table 2** Association between AKI stage and LCA-derived AKI classes

| AKI stage | Class 1 | Class 2 | Class 3 | Class 4 | p     |
|-----------|---------|---------|---------|---------|-------|
| Stage 1   | 1205 (36.3) | 455 (32.5) | 694 (28.1) | 106 (19.3) | < 0.001 |
| Stage 2   | 1912 (57.6) | 812 (58.0) | 1379 (55.9) | 152 (27.6) | < 0.001 |
| Stage 3   | 204 (6.1) | 134 (9.6) | 393 (15.9) | 292 (53.1) | < 0.001 |

Data were presented as the number (percentage). The chi-square test was used for comparison among groups. AKI, acute kidney injury; LCA, latent class analysis.

**Table 3** Association of disease severity score and outcomes with LCA-derived AKI classes

| Class 1 | Class 2 | Class 3 | Class 4 | p     |
|---------|---------|---------|---------|-------|
| SAPS II score | 37.14 ± 11.85 | 35.08 ± 13.08 | 35.66 ± 13.10 | 48.81 ± 14.03 | < 0.001 |
| SOFA score | 5.00 (3.00–7.00) | 5.00 (3.00–7.00) | 3.00 (2.00–5.00) | 6.00 (5.00–9.00) | < 0.001 |
| Elixhauser comorbidity score | 0.00 (0.00–5.00) | 1.00 (0.00–6.00) | 3.00 (0.00–8.00) | 7.00 (3.00–12.00) | < 0.001 |
| Length of ICU stay, days | 2.23 (1.29–3.92) | 2.27 (1.32–4.38) | 3.02 (1.90–5.68) | 4.07 (2.16–7.33) | < 0.001 |
| 28-day mortality | 52 (1.6) | 66 (4.7) | 375 (15.2) | 138 (25.1) | < 0.001 |

Continuous variables are presented as the SEM ± SD or median (interquartile range), as appropriate. Categorical variables are presented as numbers (percentages). The chi-square test of categorical variables and analysis of variance or the Kruskal–Wallis test of continuous variables were used for comparisons among groups. AKI, acute kidney injury; LCA, latent class analysis; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.
Comparison of prognostic prediction ability between AKI stages and AKI classes

In unadjusted model, model using AKI classes (AUC, 0.762, 95% CI 0.745–0.778) showed a significant higher AUC value than model using AKI stages (AUC, 0.678, 95% CI 0.657–0.700, p < 0.001). After adjustment, model using AKI classes (AUC, 0.860, 95% CI 0.845–0.874) also showed a significant higher AUC value than model using AKI stages (AUC, 0.806, 95% CI 0.788–0.823, p < 0.001) (Fig. 4).

Discussion

This study extracted clinical data and prognosis information for 7738 critically ill AKI patients with cardiovascular disease from the MIMIC-III database. The potential heterogeneity of AKI was well recognized, but it was unknown how to classify these AKI patients using the high-dimension clinical data. Moreover, the number as well as the clinical value of AKI subphenotypes were also unknown. Using LCA, 4 distinct AKI classes with remarkable heterogeneity were identified, and each of them had specific clinical traits. Interestingly, these new AKI classes were associated with mortality, and even had advantages in predicting prognosis compared with traditional AKI stages. To the best of our knowledge, this is the first study to use LCA to mine the potential subphenotypes of AKI in patients with severe cardiovascular disease. Our study has 3 new findings. First, 4 AKI classes were identified in patients with severe cardiovascular disease, highlighted the remarkable AKI heterogeneity in these population. Second, our study demonstrated that LCA method was feasible for mining the potential subphenotypes of AKI, raising the possibility of LCA on data mining in clinical researches. Third, these novel AKI classes showed different clinical features and better prognostic prediction ability than traditional AKI stages, which might help in clinical prognosis evaluation.

AKI is a clinical syndrome with high incidence and mortality in the ICU. The classification and prognosis assessment of AKI were mainly based on the KDIGO criteria, which include only creatinine level and urine output [11]. Our novel AKI classes were identified using clinical data and showed differences with AKI stages. Class 1 was mainly CAD patients who had undergone CABG, and thus, the pathophysiology of AKI might include cardiopulmonary bypass-induced hemodilution [12], renal ischemia reperfusion [13], and systemic inflammatory response [14]. Class 2 was mainly patients with AF, who had the highest use rate of ventilation, sedatives, and furosemide. In addition, the rate of cardiopulmonary bypass among these patients was 77.7%. AKI in class 2 might be induced by acute tubular necrosis and embolic events caused by hemodynamic instability [15] and anticoagulation-related nephropathy [16]. Class 4 was similar to stage 3 by the KDIGO criteria, which is characterized by the highest creatinine level and lowest urine output with the highest 28-day mortality. After further adjustment, the risk of 28-day mortality remained significant compared with class 1 mortality. In addition, the mortality

Table 4 Prognostic difference among the 4 AKI classes by multivariable logistic regression

| Model 1 | OR      | 95% CI       | p     |
|---------|---------|--------------|-------|
| Class 1 Reference                               |        |              |       |
| Class 2 | 3.29    | 2.27–4.79    | <0.001|
| Class 3 | 10.97   | 8.15–14.77   | <0.001|
| Class 4 | 20.37   | 14.54–28.53  | <0.001|

| Model 2 | OR      | 95% CI       | p     |
|---------|---------|--------------|-------|
| Class 1 Reference                               |        |              |       |
| Class 2 | 3.03    | 2.09–4.14    | <0.001|
| Class 3 | 9.29    | 6.88–12.54   | <0.001|
| Class 4 | 10.72   | 7.52–15.30   | <0.001|

| Model 3 | OR      | 95% CI       | p     |
|---------|---------|--------------|-------|
| Class 1 Reference                               |        |              |       |
| Class 2 | 2.98    | 2.03–4.36    | <0.001|
| Class 3 | 16.21   | 11.83–22.18  | <0.001|
| Class 4 | 8.31    | 5.75–12.02   | <0.001|

Multivariable logistic regression was used to evaluate the association between 28-day mortality and AKI classes, in which class 1 was used as a reference. Model 1 was adjusted for age, body mass index, and male sex. Model 2 was adjusted for model 1 plus AKI stage. Model 3 was adjusted for Model 2 plus SAPS II score, SOFA score, and Elixhauser comorbidity score. AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.
Conclusion

In conclusion, LCA was feasible for AKI classification in critically ill patients with cardiovascular disease, and 4 distinct subphenotypes of AKI patients with different prognoses were identified. Our results highlighted the potential heterogeneity of AKI patients, which is worthy of further investigation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-022-02587-9.

Additional file 1: Table S1. The association between each variable and 28-day mortality by univariate logistic regression.

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Author contributions

YQH and ZCX wrote the main manuscript text. YX, SXZ and TH.Y prepared the Figs. 1–4. ZXG, DS and AQS prepared the Tables 1–4. YXC, SXC, QG, and JFW designed the study and proposed amendments to the manuscript. All authors made significant contribution to this study and reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Data in this study were obtained from the Medical Information Mart for Intensive Care (MIMIC-III) database (https://physionet.org/content/mimiciii/1.4/). December 23, 2021, which is a freely accessible critical care database contained large number of clinical and trial data from the real world.

Declarations

Ethics approval and consent to participate

The use of the MIMIC-III database was approved by the review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Ethical approval was obtained from the Sun Yat-sen Memorial Hospital, Sun Yat-sen University ethics committee. All subjects/legal guardians gave written informed consent and assent as appropriate. The protocol was performed in accordance with the Declaration of Helsinki.
Consent to publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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