Derivation of "specific population who could benefit from Rosuvastatin": A secondary analysis on randomised controlled trial to uncover novel value of Rosuvastatin for precise treatment of ARDS

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Abstract

Background The high heterogeneity of ARDS contributes to paradoxical conclusions from previous investigations of rosuvastatin for ARDS. Identification of the population (phenotype) who could benefit from rosuvastatin is a novel exploration for precise treatment of ARDS. Methods The patient population for this analysis consisted of unique patients with ARDS enrolled in the SAILS trial (Rosuvastatin vs. Placebo). Phenotypes were derived using consensus k means clustering applied to routinely available clinical variables within 6 hours of hospital presentation before receiving placebo or rosuvastatin. Kaplan–Meier statistic was used to estimate the 90 day cumulative mortality for screening specific population who could benefit from rosuvastatin, with cut-off value as P <0.05. Results The derivation cohort included 585 patients with ARDS. Of the 4 derived phenotypes, phenotype 3 was identified as "specific population who could benefit from rosuvastatin" since rosuvastatin resulted in a significant reduction in 90 day cumulative mortality for ARDS (hazard ratio [HR] 0.29 [95% CI 0.09, 0.93]; P=0.027). Meanwhile, there were no significant differences in baseline characteristics between those assigned to rosuvastatin and those assigned to placebo. Additionally, rosuvastatin markedly improved the free of cardiovascular failure (10.08±3.79 in Rosuvastatin group vs 7.31±4.94 in Placebo group, P=0.01) and coagulation abnormality (13.65±1.33 vs 12.15±3.77, P=0.02) to day 14 in phenotype 3. Patients classified as phenotype 3 exhibited but not limited to the relative higher platelet count (390.05±79.43×10^9/L), lower CRP (20.23±11.99μg/L) and Creat (1.42±1.08 mg/dl), compared with patients classified as other phenotypes. Besides that, rosuvastatin seemed to increase 90 day mortality for patients in phenotype 4 (HR 2.76[95% CI 0.09, 9.93], P=0.076), with its adverse effect on the reduction of free of renal failure to day 14(4.70±4.99 vs 10.17±4.69, P=0.01). Patients in phenotype 4 showed a relative severe illness baseline features particularly renal failure. Conclusions This secondary analysis of SAILS trial identified the specific population who can benefit from rosuvastatin using machine learning applied to clinical variables at the time of hospital presentation, which uncovered a novel value of rosuvastatin for the treatment of ARDS, with validation clinical trials to be warranted to assess these further.

Introduction

Acute respiratory distress syndrome (ARDS) is a highly heterogeneous and complicated critical illness. Despite advances in clinical management, the mortality of severe ARDS remain as high as 40–46%, due to the lack of targeted therapeutic protocols for distinct patients. To categorize ARDS for furthermore appropriate therapy is the critical unmet need for precise treatment and improvement for salvage rate of ARDS. [1–2]

In consideration of rosuvastatin's anti-inflammatory effects and pathogenesis of ARDS(inadequate control of inflammatory responses in lung), rosuvastatin was attempted to be utilized in the treatment for ARDS in the last decade.[3–7] The previous studied demonstrated that rosuvastatin could improve outcomes of ARDS in animal models.[8–10] Unfortunately, a large multicenter randomized controlled trail
(RCT) in 2014 conducted by Jonathon et al. (named SAILS trial) suggested that rosuvastatin therapy did not improve clinical outcomes in patients with ARDS.[11]

The cordial reason to these paradoxical conclusions is the heterogeneity of ARDS. ARDS, as an overly broad definition of syndrome, encompasses a vast, multidimensional array of clinical and biological features. Markedly differed from experimental animals, patients with ARDS actually consist of diverse phenotypes, which appear different clinical characteristics, immune status, biological processes and severity. Several investigations successfully classified ARDS to distinct subgroups via biomarkers or clinical features [12–13], which indicated that appropriate therapies for distinct patients may be the promising strategy for precise treatment in ARDS. Rosuvastatin, as an immunomodulatory intervention to attenuate inflammation, may just benefits some specific population.

Obviously, there is a robust need to explore the novel ARDS phenotype (who could benefit from rosuvastatin) to optimize therapeutic strategy for ARDS and reduce mortality furthermore. Fortunately, the Jonathon et al. had uploaded the original data of SAILS trial to ARDS-Net database, made it possible for us to perform secondary analysis to find specific population who could benefit from rosuvastatin. Thus, we aimed to derive ARDS phenotype by using unsupervised clustering algorithm, in order to uncover novel value of Rosuvastatin for precise treatment of ARDS.

**Method**

This study was reviewed and approved by Institutional Ethics Committee of Zhongda Hospital. Institutional Ethics Committee of Zhongda Hospital and conducted under several data use agreements. The Ethical approval was shown in e-Figure 1. The data for the ARDSnet project were obtained under a waiver of informed consent and with authorization under the Health Insurance Portability and Accountability Act.

**Patient Population**

The patient population for this analysis consisted of unique patients with ARDS enrolled in the SAILS trial (Rosuvastatin vs. Placebo), which was published in 2014. The diagnostic criterion of ARDS in the SAILS trial was referenced to the Berlin definition of ARDS in 2012 [1-2]. To eliminate influence of immunosuppression on evaluation of rosuvastatin for ARDS, the patients were distinguished into 160 definitely immunosuppressed patients and 585 other patients for respective analysis. The definitely immunosuppressed patients included ARDS patients with the comorbidity of Acquired immune deficiency syndrome, Leukemia, Non-Hodgekins Lymphoma, cancer receiving chemotherapy, or patients receiving therapy of immune suppression in past 6 months. After excluding 160 definitely immunosuppressed patients, 585 other patients were enrolled in the derivation cohort for further unsupervised clustering analysis.

**Screen Clinical Features for Phenotyping**
Based on the database of SAILS trial, we firstly extracted the available variables within the first 6 hours of hospital presentation before receiving placebo or rosuvastatin, and excluded variables with missing rate greater than 10%. These clinical available characteristics included age, alanine aminotransferase, APACHE III score, aspartate aminotransferase, blood urea nitrogen, C-reactive protein, creatine kinase, creatinine, diastolic BP, Glasgow Coma Scale, height, heart rate, male sex, Paco2, Pao2:Fio2 mmHg, Pao2, platelet count, predicted body weight, respiration rate, serum albumin highest, serum albumin lowest, serum glucose lowest, shock at baseline, systolic BP, temperature, urineout and weight.

Furthermore, to screen candidate variables for identification of "specific population who can benefit from rosuvastatin ", we conducted differential analysis by using t-test on clinical available variables between Rosuvastatin group and placebo group from survival patients, P <0.3 as the threshold value.

**Statistical Methods**

To derive the phenotypes, we first assessed the candidate variable distributions, missingness, and correlation. Multiple imputation with chained equations was used to account for missing data.[14]

In order to identify different phenotypes of ARDS, the consensus k means clustering through candidate variables was utilized to perform consistent clustering on 585 patients in derivation cohort.[15] The clustering was performed using 100 iterations, with each iteration containing 80% of samples. The optimal clustering strategy was determined by cumulative distribution function curves of the consensus score, clear separation of the consensus matrix heatmaps, characteristics of the consensus cumulative tribution function plots, and adequate pair wise–consensus values between cluster members.

To evaluate the effect of rosuvastatin for outcomes of ARDS in different subgroups, Kaplan–Meier statistic was used to estimate the 90 day mortality. Organ failure free days to day 14(day), free of cardiovascular failure to day14 (day), free of coagulation abnormality to day14 (day), free of hepatic failure to day 14(day), free of renal failure to day 14(day), ICU free days to day 28(day) and ventilator free days to day 28 were analyzed by means of analysis of variance. 28 day mortality, 60 day mortality and 90 day mortality were analyzed by chi-square test. P value less than 0.05 was set as threshold value to screen significant results.

To observe the clinical features variations in different phenotypes, means of analysis of variance and chi-square test were utilized to assess the continuous variables and dichotomous variable respectively, with cut-off value as P <0.05.

The brief analysis flow plots were illuminated in e-Figure 2.

**Software and versions**

R x64 3.6.1 was conducted to process data, analyze data and plot diagrams.

**Results**
Patients

A total of 745 patients met ARDS criteria were enrolled in final analysis, with 379 patients in Rosuvastatin group and 366 patients in Placebo group. The age of patients investigated ranged from 18 to 89 (median 54) with 51% male. The mean Pao2:Fio2 level was 143.48mmHg (standard deviation [SD], 63.57mmHg) and the mean APACHE III score was 93.42 (SD, 20.15mmHg). Detailed baseline demographic and clinical characteristics were shown in supplemental electrical data-Table 1 (e-Table 1) and e-Table 2.

Derive ARDS phenotypes and identify specific population who can benefit from rosuvastatin

After differential analysis on clinical available variables, we finally screened serum glucose highest, C-reactive protein and platelet count as candidate variables for further unsupervised clustering analysis, shown in e-Table 3.

After excluding 160 definitely immunosuppressed patients, 585 patients were enrolled in derivation cohort. The consensus k means clustering models suggested that a 4-class model was the optimal fit with the 4 phenotypes, since the clearest separation of the consensus matrix heatmap could be found in the 4-class model, shown in Figure 1.

According to Kaplan–Meier statistic analysis, phenotype 3 was identified as "specific population who can benefit from rosuvastatin", shown in Figure 2. In phenotype 3 cohort, rosuvastatin resulted in a significant reduction in 90 day cumulative mortality for ARDS, (hazard ratio [HR] 0.29 [95% CI 0.09, 0.93]; P=0.027). Meanwhile, there were no significant differences in baseline characteristics between those assigned to rosuvastatin and those assigned to placebo in phenotype 3 cohort. Baseline characteristics of patients in derived 4 phenotypes were shown in e-Table 4-7.

In phenotype 3 cohort, free of cardiovascular failure and coagulation abnormality to day 14 differed significantly between the two groups. Additionally, rosuvastatin resulted in a slight raise in ventilator free days to day 28 for ARDS. There were no significant between-group differences in any of the other outcomes. The above results were illuminated in Table 1.

For a better insight in patients who could benefit from rosuvastatin, we compared the clinical characteristics among different phenotypes. Patients classified as phenotype 3 appeared highest Platelet count (390.05±79.43×10^9/L) lowest CRP (20.23±11.99μg/L ) and lowest Creat (1.42±1.08 mg/dl). Additionally, other distinct clinical characteristics in different phenotypes were described in Table 2. Indeed, phenotype 3 could be identified through our 4-class model.

Characteristics and outcomes in other phenotypes

Kaplan–Meier survival analysis indicated that rosuvastatin had no effect for ARDS in cohorts of other phenotypes. In phenotype 2 cohort, rosuvastatin appeared a slight reduction in free of hepatic failure to day 14. In addition, rosuvastatin presented a moderate reduction in free of renal failure to day 14 in
phenotype 4 cohort. More details of characteristics and outcomes in other phenotypes were described in Table 1-2.

The survival curves of 4 phenotypes were shown in e-Figure 3, and the survival curves of definitely immunosuppressed patients was shown in e-Figure 4.

**Discussion**

In this secondary analysis of SAILS trial, 4 phenotypes of ARDS were derived through routinely available clinical variables at the time of hospital presentation. These phenotypes were multidimensional, heterogeneous in their demographics, clinical characteristics, several laboratory abnormalities, effect of rosuvastatin therapy, and differed with traditional patient classifications such as direct or indirect lung injury, patterns of organ dysfunction, or severity of ARDS. In phenotype 3, rosuvastatin began to exhibit benefits for patients of ARDS, compared with placebo. This conclusion highlighted the importance of characterizing the heterogeneity of ARDS and early goal-directed therapy.

To our knowledge, the current study firstly identified the specific population who can benefit from rosuvastatin, which could improve therapeutic system in ARDS to reduce mortality furthermore, with validation clinical trials to be warranted to assess these further. These patients exhibited but not limited to the relative higher platelet count (390.05 ± 79.43 × 10^9/L), lower CRP (20.23 ± 11.99 µg/L ) and Creat (1.42 ± 1.08 mg/dl), compared with other patients of ARDS. These patients probably suffered from a relative slight infection, and might benefit from rosuvastatin for its anti-inflammatory effect could restore cardiovascular failure rapidly. Indeed, current study indicated that rosuvastatin resulted in an obvious improvement in free of cardiovascular failure to day14, (7.31 ± 4.94 in Placebo vs 10.08 ± 3.79 in rosuvastatin, P = 0.01). Phenotype 3 could be identified through our machine learning constructed 4-class model rapidly. This model could be utilized to identify specific population who can benefit from rosuvastatin at the time of patient presentation to the emergency department, and thus could be useful with regard to early treatment and enrollment in clinical trials. Only routinely available data were used in the clustering models, and the phenotypes were derived from a large observational cohort to ensure generalizability.

Rosuvastatin may improve inflammatory responses possibly via modulation on platelet-dependent mechanism, which might be potential treatment pathogenesis of rosuvastatin on the novel phenotype for ARDS. It was well known that platelet plays an important role in neutrophil mediated lung injury.[16–17] The present study indicated that patients classified as phenotype 3 exhibited relative high platelet counts. Additionally, in these patients, rosuvastatin significantly improved coagulation abnormality of ARDS, compared with placebo. Therefore, we hypothesized that platelets might be involved in the pharmacological mechanism of Rosuvastatin on specific patients of ARDS, with validation experiments to be warranted to assess these related mechanism.

Rosuvastatin might be harmful for patients with definite immunosuppression. Rosuvastatin was attempted to be utilized in patients with ARDS mainly due to rosuvastatin's anti-inflammatory effects.
However, the infection is the main risk factor of ARDS, and it has been verified that was patients with immunosuppression had worse outcomes since their weak immunity hardly eliminated pathogens.[18–19] Therefore, as immunosuppressed effect of rosuvastatin, it could not benefit such patients. This study similarly exhibited a trend that patients with definite immunosuppression had a worse outcome when receiving rosuvastatin probably, shown in Fig. 1A.

Rosuvastatin seems to be harmful for patients classified as phenotype 4. Survival curves of phenotype 4 illuminated a trend that rosuvastatin resulted in a reduction in 90 day survival rate of ARDS, despite of the less rigorous confidence interval (HR 2.76[95% CI 0.09, 9.93], P = 0.076). Meanwhile, current analysis on free of renal failure to day 14 suggested that rosuvastatin might aggravate renal damage (10.17 ± 4.69 in Placebo group vs 4.70 ± 4.99 in Rosuvastatin group, P = 0.01). Patients in phenotype 4 showed but not limited to the highest APACHE III (110.18 ± 24.35), Blood urea nitrogen (38.04 ± 28.59 mmol/L), Creat (2.25 ± 1.32 mg/dl), Serum glucose 484.35 ± 154.83 (mg/dL), morbidity of shock at baseline (68%) and the lowest PaO2:FiO2 (128.61 ± 76.91 mmHg), Glasgow Coma Scale (6.46 ± 3.33). In brief, patients in phenotype 4 showed a relative severe illness baseline features particularly renal failure, and rosuvastatin might bring some worse outcomes for ARDS.

There are several limitations to the present study. Indeed, current analysis on treatment × phenotype interactions is largely limited by sample size. Therefore, these novel proof-of-concept ARDS phenotypes could be incorporated prospectively in future study designs that subsequently validate effect of rosuvastatin for ARDS.[20] In addition, for the limitation of clinical correlation analysis, the further basic experiments should be conducted to sequentially research elaborate mechanisms of rosuvastatin in ARDS indicated by our analyses.

**Conclusion**

In this secondary analysis of SAILS trial from patients with ARDS, specific population who can benefit from rosuvastatin was identified through routinely available clinical variables at the time of hospital presentation, which uncovered a novel value of Rosuvastatin for the treatment of ARDS, with validation clinical trials to be warranted to assess these further.

**Declarations**

**Ethical Approval and Consent to participate**

Not available.

**Consent for publication**

Not available.

**Availability of data and materials**
Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Shi Zhang and Haibo Qiu had full access to all of the data in the study and take responsibility for their integrity and the accuracy of the data analysis. Shi Zhang and Zhonghua Lu performed the data process, statistical analysis, and preparation of the article for publication. All authors participated in writing the article and preparing the figures.

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Tables

Table 1. Outcomes in different phenotypes

| Outcomes                           | Placebo        | Rosuvastatin   | P          |
|------------------------------------|----------------|----------------|------------|
| 28 day mortality (%)               |                |                |            |
| Phenotype 1                         | 23%            | 21%            | 0.70       |
| Phenotype 2                         | 12%            | 17%            | 0.20       |
| Phenotype 3                         | 27%            | 14%            |            |
| Phenotype 4                         | 22%            | 50%            | 0.28       |
| 60 day mortality (%)               |                |                |            |
| Phenotype 1                         | 24%            | 25%            | 1          |
| Phenotype 2                         | 14%            | 21%            | 0.21       |
| Phenotype 3                         | 31%            | 10%            | 0.07       |
| Phenotype 4                         | 28%            | 32%            | 0.20       |
| 90 day mortality (%)               |                |                |            |
| Phenotype 1                         | 24%            | 25%            | 1          |
| Phenotype 2                         | 15%            | 21%            | 0.28       |
| Phenotype 3                         | 31%            | 10%            | 0.07       |
| Phenotype 4                         | 28%            | 32%            | 0.20       |
| Organ failure free days to day 14 (day) |    |                |            |
| Phenotype 1                         | 6.16±5.14      | 6.31±5.32      | 0.83       |
| Phenotype 2                         | 8.39±5.04      | 8.21±5.16      | 0.79       |
| Phenotype 3                         | 7±5.23         | 8.83±4.62      | 0.14       |
| Phenotype 4                         | 6.72±5.13      | 3±4.62         | 0.07       |
| Free of cardiovascular failure to day 14 (day) |  |                |            |
| Phenotype 1                         | 10.37±4.80     | 10.72±4.93     | 0.57       |
| Phenotype 2                         | 9.81±4.44      | 9.19±4.67      | 0.29       |
| Phenotype 3                         | 7.31±4.94      | 10.08±3.79     | 0.01       |
| Phenotype 4                         | 7.94±4.99      | 6.20±5.51      | 0.40       |
| Free of coagulation abnormality to day 14 (day) |  |                |            |
| Phenotype 1                         | 10.83±5.12     | 14.93±9.80     | 0.38       |
| Phenotype 2                         | 13.30±2.22     | 12.90±2.81     | 0.21       |
| Phenotype 3                         | 12.15±3.77     | 13.65±1.33     | 0.02       |
| Phenotype 4                         | 10.67±5.10     | 8.10±6.10      | 0.24       |
| Free of hepatic failure to day 14 (day) |  |                |            |
| Phenotype 1                         | 11.06±4.65     | 9.89±5.36      | 0.07       |
| Phenotype 2                         | 13.29±2.46     | 12.51±3.38     | 0.04       |
| Phenotype 3                         | 11.81±4.17     | 12.83±3.01     | 0.25       |
| Phenotype 4                         | 11.50±4.85     | 7.70±6.41      | 0.09       |
| Free of renal failure to day 14 (day) |  |                |            |
| Phenotype 1                         | 10.50±4.88     | 11.45±4.25     | 0.41       |
| Phenotype 2                         | 11.74±4.22     | 11.44±4.64     | 0.60       |
| Phenotype 3                         | 10.50±4.88     | 11.45±4.25     | 0.41       |
| Phenotype 4                         | 10.17±4.69     | 4.70±4.99      | 0.01       |
| ICU free days to day 28 (day)       |                |                |            |
| Phenotype 1                         | 13.82±9.83     | 14.93±9.80     | 0.38       |
| Phenotype 2                         | 17.05±9.07     | 15.74±9.72     | 0.27       |
| Phenotype 3                         | 12.96±11.38    | 17.35±8.59     | 0.08       |
| Phenotype 4                         | 13±10.45       | 9±10.50        | 0.34       |
| Ventilator free days to day 28 (day) |  |                |            |
| Phenotype 1                         | 14.17±10.90    | 15.43±10.62    | 0.36       |
| Phenotype 2                         | 18.07±9.68     | 17.02±10.12    | 0.41       |
| Phenotype 3                         | 13.27±11.90    | 18.75±8.93     | 0.04       |
| Phenotype 4                         | 13.67±11.58    | 10.1±11.47     | 0.44       |
Organ failure free days to day 14: No. of days without failure of circulatory, coagulation, hepatic, or renal organs from Day 1 to Day 14.

Table 2. Clinical characteristics variations in different phenotypes

| Characteristics                  | Phenotype1 (n=247) | Phenotype2 (n=244) | Phenotype3 (n=66) | Phenotype4 (n=66) | P   |
|----------------------------------|--------------------|--------------------|-------------------|-------------------|-----|
| Age (year)                       | 54.07±16.72        | 53.83±16.96        | 54.52±16.64       | 56.79±13.94       | 0.84|
| Male, NO.%                       | 48%                | 51%                | 55%               | 50%               | 0.78|
| Weight (kg)                      | 85.94±28.25        | 92.23±34.78        | 92.85±30.63       | 87.36±28.59       | 0.12|
| Height (kg)                      | 168.83±10.17       | 168.89±11.41       | 169.46±10.68      | 170.39±13.26      | 0.88|
| Predicted Body Weight (kg)       | 62.74±10.87        | 62.61±11.97        | 63.03±11.18       | 64.11±13.81       | 0.93|
| APACHE III                       | 95.47±28.60        | 83.61±24.97        | 87.69±27.28       | 110.18±24.35      | <0.01|
| Temperature (°C)                 | 37.31±0.97         | 37.45±0.98         | 37.52±0.95        | 37.82±0.86        | 0.04|
| Shock, NO.%                      | 63%                | 47%                | 55%               | 68%               | <0.01|
| Respiratory rate                 | 25.10±7.20         | 25.52±7.11         | 24.95±6.03        | 24.64±5.69        | 0.84|
| PaO2 (mmHg)                      | 91.21±33.70        | 90.17±31.78        | 95.06±43.23       | 113.64±46.30      | <0.01|
| PaCO2 (mmHg)                     | 38.24±9.45         | 41.67±9.99         | 41.29±9.20        | 35.71±9.03        | <0.01|
| PaO2:FiO2                         | 139.78±61.86       | 148.64±62.31       | 139.27±65.47      | 128.61±76.91      | 0.24|
| Heart rate (beats/min)           | 96.25±19.57        | 95.17±19.05        | 94.97±18.84       | 102±19.06         | 0.34|
| Systolic BP (mmHg)               | 109.77±18.98       | 114.72±18.49       | 115.02±19.37      | 108.11±19.13      | 0.01|
| Diastolic BP (mmHg)              | 60.63±11.76        | 61.37±13.93        | 60.89±14.22       | 55.35±10.30       | 0.14|
| Glasgow Coma Scale               | 7.60±3.24          | 8.24±3.51          | 7.92±3.56         | 6.46±3.33         | 0.03|
| Alanine aminotransferase (U/liter)| 49.32±8.91         | 47.85±8.83         | 49.03±10.19       | 46.86±10.59       | 0.23|
| Aspartate aminotransferase (U/liter)| 41.72±4.32         | 42.10±5.20         | 41.29±5.69        | 40.89±5.95        | 0.45|
| Urine output within 24 hours of | 1457±1211          | 1740±1253          | 1830±1380         | 1456±1106         | 0.03|
| hospital presentation            |                    |                    |                   |                   |     |
| Blood urea nitrogen (mmol/L)     | 27.40±19.63        | 24.63±17.68        | 24.29±18.11       | 38.04±28.59       | <0.01|
| Creatine kinase (U/liter)        | 244.63±51.68       | 241.45±53.39       | 233.29±55.59      | 226.5±56.79       | 0.20|
| Creat (mg/dl)                    | 1.65±1.28          | 1.47±1.10          | 1.42±1.08         | 2.25±1.32         | <0.01|
| Serum Glucose Highest (mg/dL)    | 148.36±50.32       | 152.57±49.78       | 157.21±47.07      | 484.35±154.83     | <0.01|
| Serum Glucose Lowest (mg/dL)     | 114.44±39.74       | 125.02±40.96       | 125.56±39.65      | 186.11±116.62     | <0.01|
| Serum Albumin Highest (g/dL)     | 2.24±0.74          | 2.43±0.63          | 2.20±0.73         | 2.46±0.88         | <0.01|
| Serum Albumin Lowest (g/dL)      | 2.18±0.69          | 2.36±0.61          | 2.11±0.70         | 2.36±0.78         | <0.01|
| Platelet count (10^9/L)          | 103.79±39.97       | 222.22±41.66       | 390.05±79.43      | 176.68±94.30      | <0.01|
| CRP (μg/L)                       | 26.04±34.69        | 28.69±27.96        | 20.23±11.99       | 26.25±13.92       | 0.22|
The consensus matrix heatmaps of consensus k means clustering. Figure 1A showed the sample distribution of 4 phenotypes after consensus k means clustering. Figure 1B-I illuminated consensus matrix heatmaps of different subgroup number (k = 2, 3, 4, 5, 6, 7, 8, 9), respectively. It can be found that when k=4, the model exhibited the clearest separation of the consensus matrix heatmap.
Figure 2

Kaplan–Meier survival curves of 90 day cumulative mortality 4 phenotypes between patients receiving Rosuvastatin and patients receiving placebo. Figure 2A-D showed survival curves respectively from phenotype 1-4. In phenotype 3 cohort, Rosuvastatin resulted in a significant reduction in 90 day cumulative mortality for ARDS, (hazard ratio [HR] 0.29 [95% CI 0.09, 0.93]; P=0.027).

Supplementary Files

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