|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Pre-matching** | | | **Post-matching** | | | |
| **Variables** | **Pulmonary  failure  (n=68)** | **Mechanical ventilation (n=53)** | **Standardized  mean difference (STD)** | **Variables** | **Pulmonary  failure  (n=49)** | **Mechanical ventilation (n=49)** | **Standardized  mean difference (STD)** |
| Age | 57.13 | 60.47 | **0.288** | Age | 57.82 (10.64) | 58.82 (10.32) | **0.095** |
| Gender (male) | 77.90% | 77.40% | **0.014** | Gender | 32 ( 65.3) | 35 ( 71.4) | **0.132** |
| CLIF-C ACLF score | 54.81 | 49.62 | **0.494** | CLIF-C ACLF score | 54.09 (8.07) | 54.31 (9.02) | **0.025** |
| CLIF-OF score | 11.25 | 9.64 | **0.746** | CLIF-OF score | 11.12 (1.93) | 11.08 (1.61) | **0.023** |
| MELD-Na score | 26.83 | 23.85 | **0.328** | MELD-Na score | 27.90 (10.78) | 28.75 (6.45) | **0.096** |
| ACLF grade (%) |  |  | **0.668** | ACLF grade (%) |  |  | **<0.001** |
| 0 | 11 (16.2%) | 17 (32.1%) |  | 0 | 0 (0%) | 0 (0%) |  |
| 1 | 7 (10.3%) | 10 (18.9%) |  | 1 | 12 (24.5%) | 12 (24.5%) |  |
| 2 | 18 (26.5%) | 16 (30.2%) |  | 2 | 21 (42.9%) | 21 (42.9%) |  |
| 3 | 32 (47.1%) | 10 (18.9%) |  | 3 | 16 (32.7%) | 16 (32.7%) |  |
| **Variables** | **Pulmonary  failure  (n=68)** | **No mechanical ventilation (n=377)** | **Standardized  mean difference (STD)** | **Variables** | **Pulmonary  failure  (n=49)** | **No mechanical ventilation (n=49)** | **Standardized  mean difference (STD)** |
| Age | 57.13 | 59.85 | **0.229** | Age | 57.82 (10.64) | 60.04 (12.14) | **0.195** |
| Gender (male) | 77.90% | 69.80% | **0.187** | Gender | 65.30% | 69.40% | **0.087** |
| CLIF-C ACLF score | 54.81 | 41.62 | **1.36** | CLIF-C ACLF score | 54.09 | 53.46 | **0.081** |
| CLIF-OF score | 11.25 | 7.6 | **1.778** | CLIF-OF score | 11.12 | 10.65 | **0.25** |
| MELD-Na score | 26.83 | 22.47 | **0.374** | MELD-Na score | 27.9 | 32.47 | **0.491** |
| ACLF grade (%) |  |  | **1.602** | ACLF grade (%) |  |  | **<0.001** |
| 0 | 11 (16.2%) | 254 ( 67.4%) |  | 0 | 0 (0%) | 0 (0%) |  |
| 1 | 7 (10.3%) | 73 ( 19.4%) |  | 1 | 12 (24.5%) | 12 (24.5%) |  |
| 2 | 18 (26.5%) | 33 ( 8.8%) |  | 2 | 21 (42.9%) | 21 (42.9%) |  |
| 3 | 32 (47.1%) | 17 ( 4.5%) |  | 3 | 16 (32.7%) | 16 (32.7%) |  |
| **Variables** | **Mechanical ventilation (n=53)** | **No mechanical ventilation (n=377)** | **Standardized  mean difference (STD)** | **Variables** | **Mechanical ventilation (n=49)** | **No mechanical ventilation (n=49)** | **Standardized  mean difference (STD)** |
| Age | 60.47 | 59.85 | **0.054** | Age | 58.82 | 60.04 | **0.109** |
| Gender (male) | 77.40% | 69.80% | **0.173** | Gender (male) | 71.40% | 69.40% | **0.045** |
| CLIF-C ACLF score | 49.62 | 41.62 | **0.82** | CLIF-C ACLF score | 54.31 | 53.46 | **0.102** |
| CLIF-OF score | 9.64 | 7.6 | **1.069** | CLIF-OF score | 11.08 | 10.65 | **0.25** |
| MELD-Na score | 23.85 | 22.47 | **0.123** | MELD-Na score | 26.93 | 31.15 | **0.562** |
| ACLF grade (%) |  |  | **0.892** | ACLF grade (%) |  |  | **<0.001** |
| 0 | 17 (32.1%) | 254 (67.4%) |  | 0 | 0 (0%) | 0 (0%) |  |
| 1 | 10 (18.9%) | 73 (19.4%) |  | 1 | 12 (24.5%) | 12 (24.5%) |  |
| 2 | 16 (30.2%) | 33 (8.8%) |  | 2 | 21 (42.9%) | 21 (42.9%) |  |
| 3 | 10 (18.9%) | 17 ( 4.5%) |  | 3 | 16 (32.7%) | 16 (32.7%) |  |

**Sup. Table S1 – Balance of baseline characteristics pre- and post-matching compared between ACLF subgroups**

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**Supplementary Table S2 – Multivariate COX regression for 28-day mortality of all univariate significant variables in the ACLF cohort** (n=176)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Exp(B)** | **Lower** | **Upper** | **p-value** |
| **Pulmonary failure** | **4.904** | **2.972** | **8.092** | **<0.001** |
| **Mechanical ventilation** | **2.455** | **1.396** | **4.315** | **0.002** |
| Age at admission date | 1.025 | 1.006 | 1.045 | 0.01 |
| Sodium [mmol/L] | 0.965 | 0.937 | 0.993 | 0.015 |
| Quick [%] | 0.979 | 0.968 | 0.990 | <0.001 |
| Pleural effusion | 1.771 | 1.084 | 2.893 | 0.022 |

**Supplementary Table S3 – Multivariate COX regression for 28-day mortality of all univariate significant variables in the matched ACLF cohort** (n=147)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Exp(B)** | **Upper** | **Lower** | **p-value** |
| **Pulmonary failure** | **3.031** | **1.644** | **5.588** | **<0.001** |
| **Mechanical ventilation** | **1.655** | **1.025** | **2.673** | **0.039** |
| Creatinine [mg/dl] | 1.146 | 1.070 | 1.227 | <0.001 |
| Lactate [mmol/l] | 1.109 | 1.045 | 1.176 | 0.001 |
| Age at admission date | 1.016 | 1.002 | 1.030 | 0.02 |
| Bilirubin [mg/dl] | 1.025 | 1.002 | 1.049 | 0.032 |
| INR | 0.992 | 0.982 | 1.001 | 0.095 |
| Sodium [mmol/L] | 0.959 | 0.938 | 0.98 | <0.001 |

**Supplementary Table S4 – Summary of ROC analysis comparing predictive performance of the CLIF-C ACLF score and the calibrated CLIF-C ACLF-R score in different cohorts.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **CLIF-C ACLF-R score** | | **CLIF-C ACLF score** | |
| **First admission cohort** | **AUROC** | **95% CI** | **AUROC** | **95% CI** |
| All first admissions | 0.87 | 0.82 - 0 .91 | 0.81 | 0.75 - 0.86 |
| All ACLF and pre-ACLF | 0.84 | 0.78 - 0.89 | 0.77 | 0.71 - 0.84 |
| **Re-admission cohort** | **AUROC** | **95% CI** | **AUROC** | **95% CI** |
| All re-admissions | 0.78 | 0.70 - 0.85 | 0.70 | 0.62 - 0.78 |
| All ACLF re-admissions | 0.74 | 0.65 - 0.84 | 0.64 | 0.54 - 0.75 |
| **External cohort (Drolz et al.)** | **AUROC** | **95% CI** | **AUROC** | **95% CI** |
| All ACLF patients | 0.65 | 0.59 - 0.7 | 0.67 | 0.62 - 0.72 |
| ACLF grade 3 | 0.62 | 0.53 - 0.70 | 0.60 | 0.51 - 0.69 |
| ACLF with extrahepatic OFs | 0.62 | 0.53 - 0.70 | 0.60 | 0.51 - 0.69 |
| ACLF with >4 organ failures | 0.86 | 0.70 - 1.0 | 0.79 | 0.6 - 0.99 |

**Supplementary Table S5** **– Comparison of patient characteristics across all study cohorts**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First admission cohort  (n=498)** | | | **Re-admission cohort  (n=261)** | | | **External cohort  (n=566)** | | |
| Age, median (IQR) | 60 (52-67) | | Age, median (IQR) | 60 (53-66) | | Age, median (IQR) | 58 (51-65) | |
| Female gender, patients (%) | 141 | (28.3%) | Female gender, patients (%) | 90 | (34.5%) | Female gender, patients (%) | 216 | (39.0%) |
| **Scores** |  | | **Scores** |  | | **Scores** |  | |
| CLIF-C-ACLF, median (IQR) | 42.6 (36.8-51.4) | | CLIF-C-ACLF, median (IQR) | 44.4 (38.5-50.6) | | CLIF-C-ACLF, median (IQR) | 53.6 (45.0 - 61.1) | |
| MELD, median (IQR) | 18.5 (13.1-25.2) | | MELD, median (IQR) | 22.1 (16-26.3) | | MELD, median (IQR) | 20 (14-29) | |
| **ACLF** |  | | **ACLF** |  | | **ACLF** |  | |
| ACLF Grade 0, patients (%) | 322 | (64.7%) | ACLF Grade 0, patients (%) | 126 | (48.3%) | ACLF Grade 0, patients (%) | 159 | (28.0%) |
| ACLF Grade 1, patients (%) | 50 | (10.0%) | ACLF Grade 1, patients (%) | 72 | (27.6%) | ACLF Grade 1, patients (%) | 43 | (8.0%) |
| ACLF Grade 2, patients (%) | 67 | (13.5%) | ACLF Grade 2, patients (%) | 40 | (15.3%) | ACLF Grade 2, patients (%) | 186 | (33.0%) |
| ACLF Grade 3, patients (%) | 59 | (11.8%) | ACLF Grade 3, patients (%) | 23 | (8.8%) | ACLF Grade 3, patients (%) | 178 | (31.0%) |

**Supplementary Table S6 – Binary logistic regression on 28-day mortality in the ACLF first admission cohort (n=176, backward LR, step 4)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Exp(B)** | **Upper** | **Lower** | **p-value** |
| **CLIF-OF Respiratory score** | 1.751 | 1.082 | 2.832 | <0.05 |
| **CLIF-OF Coagulation score** | 1.718 | 1.142 | 2.586 | <0.01 |
| **CLIF-OF Kidney score** | 1.598 | 1.018 | 2.507 | <0.05 |
| **CLIF-C ACLF score** | 1.042 | 0.993 | 1.093 | 0.093 |