Table S1 Clinical Characteristics of included trials

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variables  | ALTA (n=282) | ALVEOLI (n=550) | ARDSnet1 (n=967) | ARDSnet3 (n=343) | EDEN (n=1000) | FACTT (n=1000) | Omega (n=272) | SAILS (n=745) | p |
| Age (years) | 52(42.25,63) | 50(39,65) | 50(38,65) | 49(36,66) | 52(42,63) | 49(38,60.25) | 54(43,66.25) | 55(42,66) | <0.001 |
| APACHE III | 91(71,111) | 93(75,117) | 82(68,100) | 87(71,111) | 90(71,110) | 91(71,117) | 93(70.5,111) | 91(73,112) | <0.001 |
| DFB on day 0 (ml/24 hours) | 2225(589,4422) | NA | 1810 (428, 3841) | 1745 (572, 3772) | 2036(427.5,3949.5) | 1477(-197.5,3495.5) | 2103(444.5,4533.5) | 1806(321.5,3644) | <0.001 |
| DFB on day 1(ml/24 hours) | 1643(-93,3141) | 1878(509.5,3678) |  1540(73,2993) | 1514(615.75,3209) |  1328.5(-104.5,2895.5) | 648(-1529,2513.5) | 1435(-156,2960.5) | 1227(-400,2870) | <0.001 |
| Gender (number of male; proportion) | 156(0.55) | 302(0.55) | 552(0.57) | 210(0.61) | 510(0.51) | 534(0.53) | 139(0.51) | 365(0.49) | 0.002 |
| ICU types |  |  |  |  |  |  |  |  | <0.001 |
|  Burn  | 4(0.01) | 10(0.02) | 36(0.04) | 9(0.03) | 10(0.01) | 6(0.01) | 3(0.01) | 9(0.01) |  |
|  Cardiac SICU  | 2(0.01) | 8(0.01) | 33(0.03) | 13(0.04) | 7(0.01) | 5(0) | 2(0.01) | 5(0.01) |  |
|  CCU  | 11(0.04) | 27(0.05) | 30(0.03) | 16(0.05) | 25(0.02) | 16(0.02) | 12(0.04) | 7(0.01) |  |
|  MICU  | 157(0.56) | 306(0.56) | 507(0.52) | 188(0.55) | 618(0.62) | 663(0.66) | 173(0.64) | 468(0.63) |  |
|  MICU/SICU  | 54(0.19) | 34(0.06) | 39(0.04) | 18(0.05) | 235(0.24) | 142(0.14) | 60(0.22) | 179(0.24) |  |
|  Neuro ICU  | 3(0.01) | 10(0.02) | 18(0.02) | 2(0.01) | 9(0.01) | 13(0.01) | 3(0.01) | 17(0.02) |  |
|  Other  | 4(0.01) | 21(0.04) | 23(0.02) | 3(0.01) | 10(0.01) | 11(0.01) | 4(0.01) | 8(0.01) |  |
|  SICU  | 31(0.11) | 90(0.16) | 162(0.17) | 49(0.14) | 40(0.04) | 100(0.1) | 9(0.03) | 33(0.04) |  |
|  Trauma  | 16(0.06) | 44(0.08) | 119(0.12) | 45(0.13) | 46(0.05) | 44(0.04) | 6(0.02) | 19(0.03) |  |
| Admit from  |  |  |  |  |  |  |  |  | <0.001 |
| Another Hospital  | 44(0.16) | 108(0.2) | 182(0.19) | 77(0.22) | 228(0.23) | 211(0.21) | 50(0.18) | 152(0.2) |  |
| Another Special Care Unit  | 8(0.03) | 8(0.01) | 39(0.04) | 8(0.02) | 30(0.03) | 32(0.03) | 5(0.02) | 17(0.02) |  |
| Direct Admit  | 3(0.01) | 11(0.02) | 15(0.02) | 6(0.02) | 9(0.01) | 4(0) | 5(0.02) | 11(0.01) |  |
| ER  | 121(0.43) | 166(0.3) | 248(0.26) | 112(0.33) | 427(0.43) | 353(0.35) | 124(0.46) | 291(0.39) |  |
| Floor ward  | 61(0.22) | 150(0.27) | 281(0.29) | 80(0.23) | 222(0.22) | 273(0.27) | 61(0.22) | 210(0.28) |  |
| OR  | 23(0.08) | 69(0.13) | 153(0.16) | 41(0.12) | 22(0.02) | 70(0.07) | 8(0.03) | 24(0.03) |  |
| Recovery Room  | 5(0.02) | 13(0.02) | 19(0.02) | 11(0.03) | 14(0.01) | 21(0.02) | 5(0.02) | 8(0.01) |  |
| Stepdown Unit  | 17(0.06) | 24(0.04) | 29(0.03) | 8(0.02) | 48(0.05) | 35(0.04) | 14(0.05) | 32(0.04) |  |
| Home on UAB  | 199(0.71) | 362(0.66) | 424(0.44) | 152(0.44) | 684(0.68) | 634(0.63) | 195(0.72) | 497(0.67) | <0.001 |

Note: the number of patients in each trial was reported according to the ARDSNet dataset. Continuous variables were expressed as median and interquartile range; categorical variables were expressed as the number of proportions. The comparisons among trials were performed using Kruskal-Wallis test for continuous variables and using Chi-square test. p-values were computed by Monte Carlo simulation for Fisher’s exact test.

Abbreviations: ICU: intensive care unit; SICU: surgical intensive care unit; CCU: coronary care unit; MICU: medical ICU; OR: operating room; ER: emergency room; UAB: unassisted breathing; APACHE: Acute Physiology and Chronic Health Evaluation; DFB: daily fluid balance.

Table S2 logistic regression model to explore the association of year and mortality with and without adjustment by daily fluid balance and ventilation strategy (excluding the SAILS trial)

|  |  |  |
| --- | --- | --- |
|  | Model 1# | Model 2# |
| Variables | Odds ratio (95% CI) | P value | Odds ratio (95% CI) | Odds ratio (95% CI) |
| Years (before 2000 as reference) |  |  |  |  |
|  2000 to 2005  | 0.86(0.7 to 1.05) | 0.139 | 1.09(0.81 to 1.46) | 0.575 |
|  2005 to 2010  | 0.6(0.49 to 0.74) | <0.001 | 0.82(0.6 to 1.13) | 0.223 |
|  After 2010 | 0.78(0.55 to 1.12) | 0.182 | 1.13(0.67 to 1.89) | 0.636 |
| DFB on day 1 (with each 1000 ml increase)  | NA |  | 1.07(1.04 to 1.11) | <0.001 |
| Tidal volume on day 0 (with each 1 ml/kg PBW increase)  | NA |  | 1.06(0.99 to 1.14) | 0.096 |
| Plateau pressure on day 0 (with each 10 cmH2O increase) | NA |  | 1.51(1.25 to 1.83) | <0.001 |
| PEEP on day 0 (with each 5 cmH2O increase) | NA |  | 0.83(0.7 to 0.99) | 0.038 |
| FiO2 (with each 0.1 increase) | NA |  | 1.07(1 to 1.14) | 0.038 |
| Respiratory rate (with each 10/min increase) | NA |  | 1.42(1.2 to 1.68) | <0.001 |
| Age (with each 10-year increase)  | 1.43(1.36 to 1.5) | <0.001 | 1.58(1.47 to 1.7) | <0.001 |
| APACHE III (with each 10-point increase)  | 1.3(1.26 to 1.33) | <0.001 | 1.22(1.17 to 1.28) | <0.001 |
| Gender (female as reference)  | 1.19(1.02 to 1.4) | 0.031 | 1.51(1.21 to 1.88) | <0.001 |
| ICU type (Burn unit as reference) |  |  |  |  |
|  Cardiac SICU | 0.87(0.34 to 2.25) | 0.766 | 0.69(0.16 to 3.23) | 0.629 |
|  CCU | 0.77(0.35 to 1.76) | 0.526 | 0.66(0.19 to 2.57) | 0.528 |
|  MICU | 0.8(0.42 to 1.66) | 0.536 | 0.77(0.27 to 2.63) | 0.649 |
|  MICU/SICU | 0.47(0.23 to 1) | 0.041 | 0.43(0.14 to 1.51) | 0.154 |
|  Neuro ICU | 0.8(0.31 to 2.11) | 0.648 | 1.17(0.3 to 5.06) | 0.822 |
|  Other | 0.82(0.34 to 2.04) | 0.666 | 0.78(0.22 to 3.11) | 0.706 |
|  SICU | 0.78(0.39 to 1.67) | 0.508 | 0.91(0.29 to 3.26) | 0.871 |
|  Trauma | 0.69(0.33 to 1.51) | 0.339 | 0.62(0.2 to 2.25) | 0.434 |
| Admit from (another hospital as reference) |  |  |  |  |
|  Another Special Care Unit | 1.8(1.13 to 2.86) | 0.013 | 1.44(0.76 to 2.68) | 0.257 |
|  Direct Admit | 2.04(0.94 to 4.36) | 0.068 | 1.51(0.53 to 4.18) | 0.431 |
|  ER | 1.11(0.89 to 1.4) | 0.36 | 0.95(0.69 to 1.29) | 0.731 |
|  Floor ward | 1.8(1.43 to 2.28) | <0.001 | 1.8(1.31 to 2.47) | <0.001 |
|  OR | 1.07(0.73 to 1.57) | 0.726 | 0.78(0.44 to 1.35) | 0.385 |
|  Recovery Room | 0.86(0.43 to 1.62) | 0.645 | 0.51(0.18 to 1.29) | 0.179 |
|  Stepdown Unit | 2.01(1.33 to 3.02) | 0.001 | 2.13(1.25 to 3.59) | 0.005 |

Note: # model 1 was a logistic regression model by using mortality as the response variable adjusted for age, gender, APACHE III, ICU type and admission source. The year was categorized at 2000, 2005 and 2010. Model 2 was the model 1 plus ventilation strategy on day 0 and daily fluid balance on day 1.

Abbreviations: ICU: intensive care unit; SICU: surgical intensive care unit; CCU: coronary care unit; MICU: medical ICU; OR: operating room; ER: emergency room; UAB: unassisted breathing; APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; DFB: daily fluid balance.

Table S3 logistic regression model to explore the association of year and mortality with and without adjustment by daily fluid balance and ventilation strategy (excluding patients with tidal volume>12 ml/kg)

|  |  |  |
| --- | --- | --- |
|  | Model 1# | Model 2# |
| Variables | Odds ratio (95% CI) | P value | Odds ratio (95% CI) | Odds ratio (95% CI) |
| Years (before 2000 as reference) |  |  |  |  |
|  2000 to 2005  | 0.91(0.74 to 1.12) | 0.386 | 1.14(0.85 to 1.54) | 0.389 |
|  2005 to 2010  | 0.65(0.53 to 0.79) | <0.001 | 0.82(0.59 to 1.12) | 0.210 |
|  After 2010 | 0.78(0.61 to 0.98) | 0.032 | 1.04(0.72 to 1.5) | 0.852 |
| DFB on day 1 (with each 1000 ml increase)  |  |  | 1.09(1.05 to 1.13) | <0.001 |
| Tidal volume on day 0 (with each 1 ml/kg PBW increase)  |  |  | 1.02(0.94 to 1.1) | 0.637 |
| Plateau pressure on day 0 (with each 10 cmH2O increase) |  |  | 1.57(1.31 to 1.89) | <0.001 |
| PEEP on day 0 (with each 5 cmH2O increase) |  |  | 0.76(0.64 to 0.9) | 0.001 |
| FiO2 (with each 0.1 increase) |  |  | 1.07(1.01 to 1.14) | 0.022 |
| Respiratory rate (with each 10/min increase) |  |  | 1.37(1.17 to 1.61) | <0.001 |
| Age (with each 10-year increase)  | 1.4(1.34 to 1.47) | <0.001 | 1.58(1.47 to 1.69) | <0.001 |
| APACHE III (with each 10-point increase)  | 1.29(1.25 to 1.32) | <0.001 | 1.22(1.18 to 1.28) | <0.001 |
| Gender (female as reference)  |  |  |  |  |
| ICU type (Burn unit as reference) | 1.18(1.02 to 1.37) | 0.029 | 1.43(1.16 to 1.76) | 0.001 |
|  Cardiac SICU | 0.88(0.36 to 2.19) | 0.790 | 0.62(0.15 to 2.58) | 0.507 |
|  CCU | 0.76(0.36 to 1.62) | 0.462 | 0.69(0.23 to 2.24) | 0.525 |
|  MICU | 0.75(0.41 to 1.45) | 0.375 | 0.7(0.28 to 1.97) | 0.472 |
|  MICU/SICU | 0.51(0.27 to 1.02) | 0.047 | 0.49(0.19 to 1.41) | 0.16 |
|  Neuro ICU | 0.69(0.28 to 1.68) | 0.408 | 1.03(0.3 to 3.65) | 0.968 |
|  Other | 0.76(0.32 to 1.79) | 0.524 | 0.86(0.27 to 2.87) | 0.798 |
|  SICU | 0.75(0.39 to 1.49) | 0.392 | 0.87(0.32 to 2.59) | 0.793 |
|  Trauma | 0.7(0.35 to 1.45) | 0.323 | 0.69(0.25 to 2.08) | 0.484 |
| Admit from (another hospital as reference) |  |  |  |  |
|  Another Special Care Unit | 1.98(1.28 to 3.04) | 0.002 | 1.52(0.81 to 2.8) | 0.182 |
|  Direct Admit | 2.01(1 to 3.95) | 0.045 | 1.26(0.47 to 3.27) | 0.636 |
|  ER | 1.11(0.9 to 1.38) | 0.318 | 0.92(0.68 to 1.24) | 0.567 |
|  Floor ward | 1.88(1.51 to 2.34) | <0.001 | 1.85(1.37 to 2.51) | <0.001 |
|  OR | 1.1(0.75 to 1.6) | 0.619 | 0.9(0.51 to 1.56) | 0.722 |
|  Recovery Room | 0.77(0.39 to 1.46) | 0.443 | 0.44(0.14 to 1.15) | 0.118 |
|  Stepdown Unit | 1.92(1.32 to 2.8) | 0.001 | 1.93(1.18 to 3.16) | 0.009 |

Note: # model 1 was a logistic regression model by using mortality as the response variable adjusted for age, gender, APACHE III, ICU type and admission source. The year was categorized at 2000, 2005 and 2010. Model 2 was the model 1 plus ventilation strategy on day 0 and daily fluid balance on day 1.

Abbreviations: ICU: intensive care unit; SICU: surgical intensive care unit; CCU: coronary care unit; MICU: medical ICU; OR: operating room; ER: emergency room; UAB: unassisted breathing; APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; DFB: daily fluid balance.

Table S4 estimated cause specific hazard and subdistribution hazard ratios for home with unassisted breathing using multivariable regression model

|  |  |  |
| --- | --- | --- |
|  | Fine-Gray subdistribution hazard ratio | Cause-specific hazard ratio |
|  | SHR | Lower 95% CI | Upper 95% CI | p | CSHR | Lower 95% CI | Upper 95% CI | p |
| Year before 2000 as reference |  |  |  |  |  |  |  |  |
| From 2000 to 2010 | 1.591 | 1.457 | 1.737 | <0.001 | 1.602 | 1.468 | 1.747 | <0.001 |
| After 2010 | 1.727 | 1.535 | 1.943 | <0.001 | 1.742 | 1.550 | 1.957 | <0.001 |
| Age with 1 year increase | 0.986 | 0.983 | 0.988 | <0.001 | 0.986 | 0.983 | 0.988 | <0.001 |
| APACHE III with each 10 points increase | 0.917 | 0.903 | 0.932 | <0.001 | 0.916 | 0.902 | 0.930 | <0.001 |
| Admit from (another hospital as reference) |  |  |  |  |  |  |  |  |
|  Another Special Care Unit | 1.148 | 0.935 | 1.410 | 0.190 | 1.152 | 0.914 | 1.452 | 0.231 |
|  Direct Admit | 0.670 | 0.452 | 0.994 | 0.046 | 0.669 | 0.454 | 0.985 | 0.042 |
|  ER | 1.042 | 0.941 | 1.154 | 0.430 | 1.043 | 0.947 | 1.150 | 0.392 |
|  Floor ward | 0.820 | 0.735 | 0.915 | <0.001 | 0.817 | 0.734 | 0.909 | <0.001 |
|  OR | 0.781 | 0.662 | 0.922 | 0.004 | 0.778 | 0.659 | 0.918 | 0.003 |
|  Recovery Room | 1.308 | 0.977 | 1.751 | 0.072 | 1.317 | 1.017 | 1.707 | 0.037 |
|  Stepdown Unit | 1.025 | 0.840 | 1.252 | 0.810 | 1.027 | 0.841 | 1.253 | 0.796 |
| Gender (female as reference) | 0.958 | 0.889 | 1.031 | 0.250 | 0.957 | 0.890 | 1.028 | 0.229 |
| ICU type (Burn unit as reference) |  |  |  |  |  |  |  |  |
|  Cardiac SICU | 1.480 | 0.982 | 2.229 | 0.061 | 1.492 | 0.942 | 2.361 | 0.088 |
|  CCU | 2.011 | 1.433 | 2.823 | <0.001 | 2.028 | 1.408 | 2.921 | <0.001 |
|  MICU | 1.710 | 1.318 | 2.219 | <0.001 | 1.722 | 1.271 | 2.334 | <0.001 |
|  MICU/SICU | 1.819 | 1.386 | 2.386 | <0.001 | 1.831 | 1.340 | 2.503 | <0.001 |
|  Neuro ICU | 1.327 | 0.907 | 1.942 | 0.150 | 1.330 | 0.872 | 2.029 | 0.185 |
|  Other | 1.761 | 1.228 | 2.526 | 0.002 | 1.770 | 1.182 | 2.650 | 0.006 |
|  SICU | 1.100 | 0.831 | 1.456 | 0.500 | 1.099 | 0.799 | 1.513 | 0.561 |
|  Trauma | 0.975 | 0.730 | 1.302 | 0.860 | 0.972 | 0.699 | 1.353 | 0.868 |
| DFB on day 1 per 2000 ml  | 0.918 | 0.895 | 0.942 | <0.001 | 0.917 | 0.894 | 0.940 | <0.001 |
| Vasopressor use | 0.898 | 0.828 | 0.973 | 0.008 | 0.896 | 0.828 | 0.970 | 0.007 |

Note: Death was considered as a competing risk for home on UAB because it could preclude the occurrence of home on UAB. Cause-specific Cox proportional hazard model and Fine-Gray model were built to estimate the impact of the year on the cumulative incidence of home on UAB. Covariates such as age, APACHE III, FB on day 1, locations before ICU admission, ICU type and vasopressor use were included in the models.

Abbreviations: ICU: intensive care unit; SICU: surgical intensive care unit; CCU: coronary care unit; MICU: medical ICU; OR: operating room; ER: emergency room; UAB: unassisted breathing; APACHE: Acute Physiology and Chronic Health Evaluation; SHR: subdistribution hazard ratio; CSHR: cause-specific hazard ratio; CI: confidence interval; DFB: daily fluid balance.