APPENDIX

Description of the multiple imputations

For the imputation of missing values, we used multiple imputations by chained equations. This technique uses switching regression, which is an iterative multivariable regression technique and implemented in the STATA software with the ice command (Royston P. 2005. Multiple imputation of missing values: update. Stata Journal 5: 188-201; Royston P. 2005. Multiple imputation of missing values: update of ice. Stata Journal 5: 527-536.; Royston P. 2007. Multiple imputation of missing values: further update of ice, with an emphasis on interval censoring. Stata Journal 7: 445-464.).

The following 29 variables were considered in the chained equations to impute missing values: BMI (log-transformed), respiratory compliance, oxygenation index (log-transformed), adjusted PaO2/FiO2 (log-transformed), probability of death (inverse normal transformed), respiratory rate, plateau pressure at baseline, minute ventilation at baseline (log-transformed), tidal volume at baseline (log-transformed), age, number of days on ICU before randomization, number of days of the ventilator, number of days until death in hospital, number of additional failed organs at baseline, set baseline PEEP, direct lung injury at baseline, presence of ARDS, gender, presence of severe sepsis, trial number, censoring code for death, censoring code for coming off the ventilator, group assignment, rescue therapy, death after rescue therapy, therapy with muscle relaxation, therapy with vasopressor support, therapy with steroids. According to the nature of the variable, linear regression, logistic regression or ordinal regression was used in the respective equations. We used the first imputed dataset for our analyses.

APPENDIX TABLE 1: Model parameters from meta-analysis of functions for each modifier-outcome pair adjusted for age, sepsis and predicted probability of death. FP2 denotes the fractional polynomial function for interaction with its two chosen power terms in brackets. All values are rounded to 2 decimals. BMI = body mass index, CI = confidence interval, OI = oxygenation index, OR = odds ratio, P = P value, RC = respiratory compliance, SE = standard error

	60 days in hospital mortality					Time to death					Time to unassisted breathing				
BMI		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.04	0.003	<0.001	1.03 – 1.04	Age	1.03	0.003	<0.001	1.02 – 1.03	Age	0.99	0.002	<0.001	0.99 – 1.00
	Severe sepsis	1.11	0.111	0.281	0.92 – 1.35	Severe sepsis	1.08	0.088	0.340	0.92 – 1.27	Severe sepsis	0.99	0.056	0.921	0.89 – 1.11
	Probability of death	1.03	0.002	<0.001	1.02 – 1.03	Probability of death	1.02	0.002	<0.001	1.01 – 1.02	Probability of death	0.99	0.0012	<0.001	0.99 – 1.00
	BMI interaction	FP2 (-1, 3)				BMI interaction	FP2 (0, 3)				BMI interaction	FP2 (3, 3)			
RC		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.04	0.003	<0.001	1.03 – 1.04	Age	1.03	0.003	<0.001	1.02 – 1.03	Age	0.99	0.002	<0.001	0.97 – 1.00
	Severe sepsis	1.05	0.111	0.617	0.86 – 1.30	Severe sepsis	1.09	0.088	0.305	0.93 – 1.27	Severe sepsis	1.00	0.569	0.942	0.90 – 1.12
	Probability of death	1.03	0.002	<0.001	1.02 – 1.03	Probability of death	1.02	0.002	<0.001	1.01 – 1.02	Probability of death	0.99	0.0012	<0.001	0.99 – 1.00
	RC interaction	FP2 (0, 2)				RC interaction	FP2 (-2, -0.5)				RC interaction	FP2 (-1, 3)			
PaO2/FiO2		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.03	0.003	<0.001	1.03 – 1.04	Age	1.03	0.003	<0.001	1.02 – 1.03	Age	0.99	0.002	<0.001	0.99 – 1.00
	Severe sepsis	1.07	0.114	0.513	0.87 – 1.32	Severe sepsis	1.10	0.090	0.225	0.94 – 1.29	Severe sepsis	0.99	0.560	0.907	.089 – 1.1
	Probability of death	1.02	0.002	<0.001	1.02 – 1.03	Probability of death	1.02	0.002	<0.001	1.01 – 1.02	Probability of death	0.99	0.001	<0.001	0.98 – 0.99
	PaO2/FiO2 interaction	FP2 (1, 2)				PaO2/FiO2 interaction	FP2 (1, 2)				PaO2/FiO2 interaction	FP2 (2, 2)			
OI		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.04	0.003	<0.001	1.03 – 1.04	Age	1.03	0.003	<0.001	1.02 – 1.03	Age	0.99	0.002	<0.001	0.99 – 1.00
	Severe sepsis	1.05	0.112	0.644	0.85 – 1.30	Severe sepsis	1.09	0.088	0.308	0.93 – 1.27	Severe sepsis	1.01	0.056	0.850	0.90 – 1.13
	Probability of death	1.02	0.002	<0.001	1.02 – 1.03	Probability of death	1.02	0.002	<0.001	1.01 – 1.02	Probability of death	0.99	0.001	<0.001	0.98 – 0.99
	OI interaction	FP2 (-2, 0)				OI interaction	FP2 (0.5, 3)				OI interaction	FP2 (-2, -1)			

APPENDIX TABLE 2: LOVS trial (N=983). Model parameters for each modifier-outcome pair adjusted for age, sepsis and predicted probability of death. FP2 denotes the fractional polynomial function for interaction with its two chosen power terms in brackets. All values are rounded to 2 decimals. BMI = body mass index, CI = confidence interval, FP = fractional polynomial, OI = oxygenation index, OR = odds ratio, P = P value, RC = respiratory compliance, SE = standard error

BMI

60 days in hospital mortality

	OR	SE	P	95% CI
Age	1.04	0.005	<0.001	1.03 – 1.05
Severe sepsis	1.11	0.174	0.498	0.82 – 1.51
Probability of death	1.03	0.004	<0.001	1.02 – 1.04
BMI interaction	FP2 (-2, -1)			

Time to death

	HR	SE	P	95% CI
Age	1.03	0.004	<0.001	1.02 – 1.04
Severe sepsis	1.09	0.125	0.471	0.87 – 1.36
Probability of death	1.02	0.003	<0.001	1.02 – 1.03
BMI interaction	FP2 (1, 1)			

Time to unassisted breathing

	HR	SE	P	95% CI
Age	0.99	0.002	<0.001	0.99 – 1.00
Severe sepsis	0.96	0.082	0.637	0.81 – 1.14
Probability of death	0.99	0.002	<0.001	0.98 – 0.99
BMI interaction	FP2 (3, 3)			

RC

	OR	SE	P	95% CI
Age	1.04	0.005	<0.001	1.03 – 1.05
Severe sepsis	1.14	0.179	0.416	0.84 – 1.54
Probability of death	1.03	0.004	<0.001	1.02 – 1.04
RC interaction	FP2 (-2, -1)			

	HR	SE	P	95% CI
Age	1.03	0.004	<0.001	1.02 – 1.04
Severe sepsis	1.13	0.129	0.300	0.90 – 1.41
Probability of death	1.02	0.002	<0.001	1.02 – 1.03
RC interaction	FP2 (-2, -2)			

	HR	SE	P	95% CI
Age	0.99	0.002	<0.001	0.98 - 0.99
Severe sepsis	0.97	0.0833	0.718	0.82 – 1.15
Probability of death	0.99	0.002	<0.001	0.98 – 0.99
RC interaction	FP2 (-0.5, 1)			

PaO2/FiO2

	OR	SE	P	95% CI
Age	1.04	0.005	<0.001	1.03 – 1.05
Severe sepsis	1.16	0.186	0.356	0.85 – 1.59
Probability of death	1.03	0.004	<0.001	1.02 – 1.04
PaO2/FiO2 interaction	FP2 (1, 2)			

	HR	SE	P	95% CI
Age	1.03	0.004	<0.001	1.02 – 1.04
Severe sepsis	1.13	0.131	0.278	0.90 – 1.42
Probability of death	1.02	0.003	<0.001	1.02 – 1.03
PaO2/FiO2 interaction	FP2 (0, 3)			

	HR	SE	P	95% CI
Age	0.99	0.002	<0.001	0.80 – 1.12
Severe sepsis	0.95	0.0812	0.550	0.82 – 1.15
Probability of death	0.99	0.002	<0.001	0.98 – 0.99
RC interaction	FP2 (3, 3)			

OI

	OR	SE	P	95% CI
Age	1.04	0.005	<0.001	1.03 – 1.06
Severe sepsis	1.17	0.187	0.343	0.85 – 1.60
Probability of death	1.03	0.004	<0.001	1.02 – 1.03
OI interaction	FP2 (-2, 3)			

	HR	SE	P	95% CI
Age	1.03	0.004	<0.001	1.02 – 1.04
Severe sepsis	1.13	0.131	0.277	0.90 – 1.42
Probability of death	1.02	0.003	<0.001	1.02 – 1.03
OI interaction	FP2 (-2, 3)			

	HR	SE	P	95% CI
Age	0.99	0.002	<0.001	0.99 – 1.00
Severe sepsis	0.90	0.078	0.221	0.76 – 1.07
Probability of death	0.99	0.002	<0.001	0.98 – 0.99
RC interaction	FP2 (-2, 0.5)			

APPENDIX TABLE 3: EXPRESS trial (N=767). Model parameters for each modifier-outcome pair adjusted for age, sepsis and predicted probability of death. FP2 denotes the fractional polynomial function for interaction with its two chosen power terms in brackets. All values are rounded to 2 decimals. BMI = body mass index, CI = confidence interval, FP = fractional polynomial, OI = oxygenation index, OR = odds ratio, P = P value, RC = respiratory compliance, SE = standard error

	60 days in hospital mortality					Time to death					Time to unassisted breathing				
BMI		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.03	0.006	<0.001	1.02 – 1.05	Age	1.02	0.005	<0.001	1.02 – 1.03	Age	0.99	0.003	<0.001	0.98 - 0.99
	Severe sepsis	0.92	0.175	0.664	0.63 – 1.34	Severe sepsis	1.00	0.148	0.954	0.74 – 1.33	Severe sepsis	1.05	0.117	0.672	0.84 – 1.30
	Probability of death	1.02	0.003	<0.001	1.01 – 1.02	Probability of death	1.01	0.002	<0.001	1.01 – 1.02	Probability of death	0.99	0.002	0.048	0.99 – 1.00
	BMI interaction	FP2 (-2, -2)				BMI interaction	FP2 (-2, -1)				BMI interaction	FP2 (-2, -2)			
RC		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.03	0.006	<0.001	1.02 – 1.05	Age	1.02	0.005	<0.001	1.01 – 1.03	Age	0.99	0.003	<0.001	0.98 - 0.99
	Severe sepsis	0.98	0.186	0.916	0.68 – 1.42	Severe sepsis	1.02	0.153	0.876	0.76 – 1.37	Severe sepsis	1.09	0.118	0.441	0.88 – 1.35
	Probability of death	1.02	.003	<0.001	1.01 – 1.02	Probability of death	1.01	0.003	<0.001	1.01 – 1.02	Probability of death	0.99	0.002	0.020	0.99 – 1.00
	RC interaction	FP2 (-2, 3)				RC interaction	FP2 (-2, 3)				RC interaction	FP2 (-2, 3)			
PaO2/FiO2		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.03	0.006	<0.001	1.02 – 1.04	Age	1.02	0.005	<0.001	1.01 – 1.03	Age	0.99	0.003	<0.001	0.98 - 0.99
	Severe sepsis	1.01	0.192	0.948	0.70 – 1.47	Severe sepsis	1.06	0.157	0.701	0.79 – 1.42	Severe sepsis	1.09	0.118	0.441	0.88 – 1.35
	Probability of death	1.01	0.003	<0.001	1.01 – 1.02	Probability of death	1.01	0.003	<0.001	1.01 – 1.02	Probability of death	0.99	0.002	0.020	0.99 – 1.00
	PaO2/FiO2 interaction	FP2 (0.5, 2)				PaO2/FiO2 interaction	FP2 (1, 2)				PaO2/FiO2 interaction	FP2 (-2, 3)			
OI		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.03	0.006	<0.001	1.02 – 1.05	Age	1.02	0.005	<0.001	1.02 – 1.03	Age	0.99	0.003	<0.001	0.99 – 1.00
	Severe sepsis	.99	0.190	0.959	0.68 – 1.44	Severe sepsis	1.04	0.154	0.817	0.77 – 1.38	Severe sepsis	1.19	0.1211	0.344	0.90 – 1.37
	Probability of death	1.01	0.003	<0.001	1.01 – 1.02	Probability of death	1.01	0.003	<0.001	1.01 – 1.02	Probability of death	0.99	0.002	0.077	0.99 – 1.00
	OI interaction	FP2 (-2, 2)				OI interaction	FP2 (-2, 2)				OI interaction	FP2 (-2, 2)			

APPENDIX TABLE 4: ALVEOLI trial (N=549). Model parameters for each modifier-outcome pair adjusted for age, sepsis and predicted probability of death. FP2 denotes the fractional polynomial function for interaction with its two chosen power terms in brackets. All values are rounded to 2 decimals. BMI = body mass index, CI = confidence interval, FP = fractional polynomial, OI = oxygenation index, OR = odds ratio, P = P value, RC = respiratory compliance, SE = standard error

	60 days in hospital mortality					Time to death					Time to unassisted breathing				
BMI		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.03	0.007	<0.001	1.02 – 1.05	Age	1.03	0.005	<0.001	1.02 – 1.04	Age	0.99	0.003	0227	0.99 – 1.00
	Severe sepsis	1.00	0.2250	0.996	1.03 – 1.06	Severe sepsis	1.09	0.191	0.605	0.78 – 1.54	Severe sepsis	0.95	0.104	0.620	0.76 – 1.17
	Probability of death	1.04	0.0060	<0.001	1.03 – 1.06	Probability of death	1.04	0.005	<0.001	1.03 – 1.05	Probability of death	0.99	0.003	<0.001	0.98 – 0.99
	BMI interaction	FP2 (3, 3)				BMI interaction	FP2 (3, 3)				BMI interaction	FP2 (-2, 3)			
RC		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.03	0.007	<0.001	1.02 – 1.05	Age	1.03	0.006	<0.001	1.02 – 1.04	Age	0.99	0.003	0.076	0.99 – 1.00
	Severe sepsis	0.97	0.218	0.889	0.62 – 1.51	Severe sepsis	1.06	0.185	0.727	0.76 – 1.50	Severe sepsis	1.00	0.111	0.981	0.81 – 1.25
	Probability of death	1.04	0.006	<0.001	1.03 – 1.06	Probability of death	1.04	0.005	<0.001	1.03 – 1.04	Probability of death	0.99	0.003	<0.001	0.98 – 0.99
	RC interaction	FP2 (3, 3)				RC interaction	FP2 (3, 3)				RC interaction	FP2 (0.5, 3)			
PaO2/FiO2		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.03	0.007	<0.001	1.02 – 1.05	Age	1.03	0.006	<0.001	1.02 – 1.04	Age	1.00	0.003	0.278	0.99 – 1.00
	Severe sepsis	0.98	0.223	0.923	0.63 – 1.53	Severe sepsis	1.09	0.191	0.636	0.77 – 1.53	Severe sepsis	0.98	0.108	0.863	0.79 – 1.22
	Probability of death	1.04	0.006	<0.001	1.03 – 1.05	Probability of death	1.03	0.005	<0.001	1.02 – 1.04	Probability of death	0.99	0.003	<0.001	0.98 – 0.99
	PaO2/FiO2 interaction	FP2 (-2, -2)				PaO2/FiO2 interaction	FP2 (-2, -2)				PaO2/FiO2 interaction	FP2 (-2, -2)			
OI		OR	SE	P	95% CI		HR	SE	P	95% CI		HR	SE	P	95% CI
	Age	1.04	0.007	<0.001	1.02 – 1.05	Age	1.03	0.006	<0.001	1.02 – 1.04	Age	0.99	0.003	0.034	0.99 – 1.00
	Severe sepsis	0.91	0.210	0.681	0.58 – 1.43	Severe sepsis	1.03	0.179	0.882	0.73 – 1.44	Severe sepsis	1.01	0.112	0.898	0.82 – 1.26
	Probability of death	1.04	0.006	<0.001	1.03 - 1.05	Probability of death	1.03	0.005	<0.001	1.02 – 1.04	Probability of death	0.99	0.003	<0.001	0.98 – 0.99
	OI interaction	FP2 (3, 3)				OI interaction	FP2 (3, 3)				OI interaction	FP2 (-1, -1)			