Online-only material belonging to:

A model for case-mix adjustment for comparison of outcomes in mechanically ventilated patients using electronic routine care data

M.S.M. van Mourik, K.G.M. Moons, MICU Registry, M.V. Murphy, M.J.M. Bonten, M. Klompas
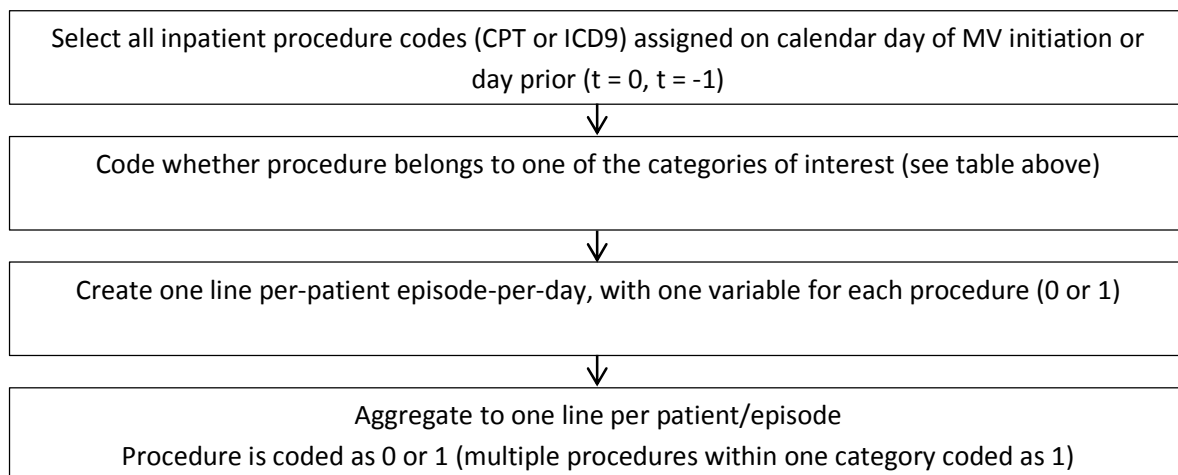
Contents:

Section 1: Variable specifications

A. Procedure codes

Classification of procedure categories

Category	Description, notes	Codes included
Muscoskeletal	Procedure to muscoskeletal system. Excludes casts, strapping	CPT: 20000-28899, 29800-29999, ICD9: 21, 03.53, 76-84
Thorax	Procedure to thorax: lungs or mediastinal space. Excludes tracheostomy, bronchoscopy, lung or heart transplantation, thoracocentesis	CPT: 32000-32850, 32900-32999, 39000-39599. ICD9: 32-33.1, 33.3-33.49, 33.7-34.91, 34.92-34.99.
Heart or Lung transplant	Heart or Lung transplantation	CPT: 32850-32856, 33945, 33935 ICD9: 33.5, 37.51, 33.5
Valve	Valve replacement procedure	CPT: 33400-33499 ICD9: 35.0-35.3
CABG	Coronary artery bypass graft	CPT: 35500 – 33573 ICD9: 36.1
Aneurysm	Aneurysm procedure (irrespective of location)	CPT: 33860-33909, 34800-35179 ICD9: 39.71, 39.73, 39.79, 38.43-38.49
Procedure of digestive tract	Procedure to the esophagus, stomach, intestine, liver, biliary system, pancreas, anus, abdominal wall. Incl. (diagnostic) endoscopies, gastrostomy and other types of stoma.	CPT: 43020 – 43659, 43800 – 50000. ICD9: 17.0-17.3, 42 – 54 (excl 43.1)
Spleen	Procedure to spleen or splenectomy	CPT: 38100-38201 ICD9: 41.2, 41.4 - 41.5
Cranial	Procedure to skull or brain, including burr holes	CPT: 61000-62257 ICD9: 1 – 2, ICD9 7.5 - 7.7

Flowchart processing of procedure information:

Select all inpatient procedure codes (CPT or ICD9) assigned on calendar day of MV initiation or day prior (t = 0, t = -1)

↓

Code whether procedure belongs to one of the categories of interest (see table above)

↓

Create one line per-patient episode-per-day, with one variable for each procedure (0 or 1)

↓

Aggregate to one line per patient/episode
Procedure is coded as 0 or 1 (multiple procedures within one category coded as 1)

B. Laboratory information

Flowchart processing of laboratory information:

Select all inpatient laboratory tests of interest performed on calendar day of MV initiation or day prior (t = 0, t = -1), see table below

↓

Analyze data for data integrity and where necessary perform corrections

↓

Remove duplicates by selecting most abnormal value per patient/episode per day

↓

Aggregate to one line per patient/episode (selecting most abnormal)

↓

Outlier values: Replace values below the 1st percentile with the 1st percentile value and values above the 99th percentile with the 99th percentile value (cap & floor). For values used in model development, refer to table below.

↓

Perform multiple imputation (after merging of files, using all predictors and outcome)

↓

Create restricted cubic splines or transform variables where necessary (4 knots spline at default locations - table below)

Parameter specifications laboratory variables

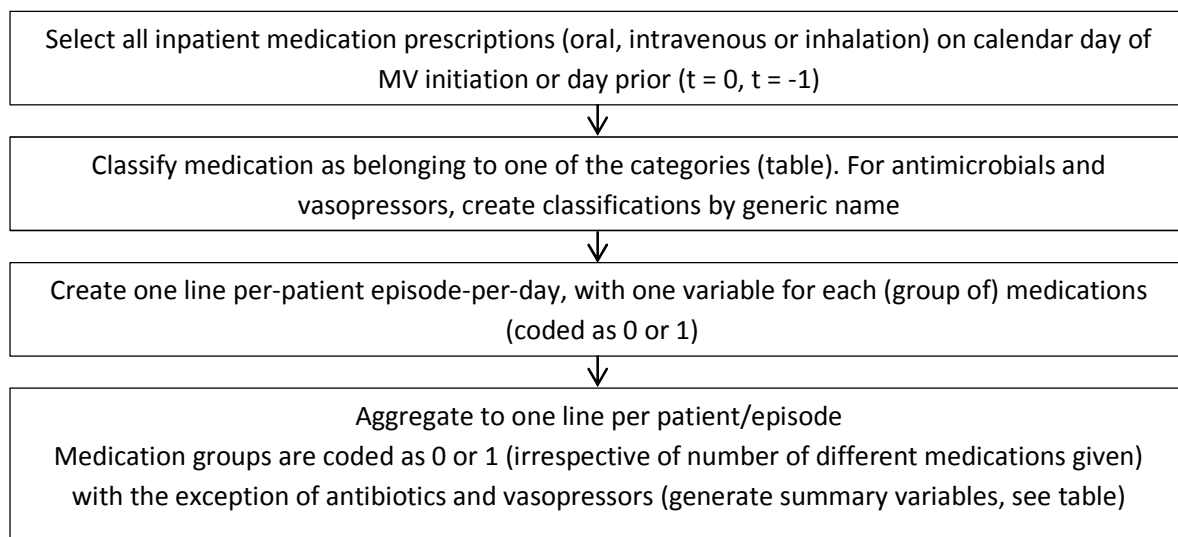| Parameter	Unit	Lowest or highest [a]	P1;P99 (cap & floor)	Spline knot locations if applicable[b]
Physiology I				
Hematocrit	%	Lowest	16.3; 45.1	20; 28.2; 40 (3 knots)
White blood cell count	10^3/uL	Lowest	0.61; 29.65	3.15; 7.29; 10.43; 19.13
Platelet count	10^3/uL	Lowest	15; 588	51; 130; 193; 367
Creatinine	mg/dL	Highest	0.39; 7.06	0.57; 0.88; 1.17; 3.19
Blood urea nitrogen	mg/dL	Highest	6; 114	--
Glucose	mg/dL	Lowest	35; 236	63; 94; 111; 164
Sodium	mmol/L	Highest	129; 154	134; 139; 141; 147
INR	-	Highest	1.0; 5.1	--
Physiology II				
Albumin	g/dL	Lowest	1.4; 4.7	--
SGPT	U/L	Highest	5; 1529	--
Total bilirubin	mg/dL	Highest	0.2; 13.6	--
Physiology III				
pO2	mmHg	Lowest	37; 418	55; 92; 127.3; 265;
pCO2	mmHg	Lowest	19; 62	26; 34; 38; 47
pH	--	Lowest	7.0; 7.5	7.15; 7.3; 7.35; 7.44

Abbreviations: INR – international normalized ratio, SGPT - serum glutamic-pyruvic transaminase (or ALAT), pO2 = partial oxygen pressure, pCO2 = partial carbon dioxide pressure.

[a]: For all physiology variables, the values most likely associated with a poor patient outcome was selected; depending on the specific variable this can be the lowest or the highest value.

[b]: Software to determine knot locations and create spline variables obtained from the *rms*() package in R, and SAS macros from: http://biostat.mc.vanderbilt.edu/wiki/Main/SasMacros, in particular %rcspline() (last accessed 11-11-2013).

C. Medications

Flowchart processing of medication information

Select all inpatient medication prescriptions (oral, intravenous or inhalation) on calendar day of MV initiation or day prior (t = 0, t = -1)

↓

Classify medication as belonging to one of the categories (table). For antimicrobials and vasopressors, create classifications by generic name

↓

Create one line per-patient episode-per-day, with one variable for each (group of) medications (coded as 0 or 1)

↓

Aggregate to one line per patient/episode Medication groups are coded as 0 or 1 (irrespective of number of different medications given) with the exception of antibiotics and vasopressors (generate summary variables, see table)

Medications included in prediction models.

Medication as predictor	Coded as:
Antibiotic	Codes as 2 or more started yes/no (classified by generic active compound)
Antifungal	Yes/no
Amiodarone	Yes/no
Vasopressor	Nr of different pressors started
Anticonvulsant	Yes/no
Steroid	Yes/no
Vitamin K	Yes/no
Airway medication (inhaled)	Yes/no
Antipsychotic	Yes/no

Notes: for all medications, only medication *started* on t = -1 or t = 0 are included.

Section 2: Model results

Table S1: Parameter estimates for model 2, after internal validation and uniform shrinkage.

	Estimate	Standard error	Odds ratio	Lower 95% CI	Upper 95% CI
Intercept	9,237	2.088	Na	Na	Na
Age	0,026	0,002	1,026	1,023	1,030
Female	-0,040	0,051	0,961	0,870	1,061
Unit group (Medical = reference)					
- Surgical	-0,556	0,112	0,573	0,461	0,714
- Neurology	0,650	0,103	1,916	1,566	2,344
- CV surgery	-1,880	0,221	0,153	0,099	0,235
Time to MV (day of admission = reference)					
- Day 1 or 2 after admission	0,154	0,092	1,166	0,974	1,397
- Days 3-7 after admission	0,748	0,112	2,111	1,698	2,629
- >= 8 days after admission	0,862	0,122	2,368	1,864	3,008
Blood culture (obtained)	0,184	0,057	1,202	1,075	1,344
Procedures (>1 possible):					
Muscoskeletal	-0,726	0,110	0,484	0,390	0,600
Thorax	0,303	0,176	1,354	0,959	1,912
Lung or heart transplant	-1,640	0,373	0,194	0,093	0,403
Cardiac valve	-1,036	0,189	0,355	0,245	0,514
CABG	-1,230	0,210	0,292	0,193	0,442
Aneurysm	-0,583	0,169	0,558	0,401	0,777
Digestive tract	-0,651	0,135	0,522	0,400	0,680
Cranial	0,890	0,451	2,435	1,006	5,892
Laboratory variables					
Hematocrit (min)	0,011	0,011	1,011	0,99	1,032
Spline	-0,007	0,014	0,993	0,967	1,02
White blood cells (min)	-0,079	0,023	0,924	0,884	0,966
Spline 1	0,496	0,110	1,642	1,324	2,037
Spline 2	-1,282	0,307	0,277	0,152	0,506
Platelets (min)	-0,012	0,001	0,988	0,986	0,991
Spline 1	0,032	0,006	1,033	1,02	1,046
Spline 2	-0,070	0,017	0,932	0,901	0,965
Creatinine (max)	-0,825	0,296	0,438	0,245	0,783
Spline 1	22,755	4,648	$7,63 \times 10^{9}$	843945.6	$6,89 \times 10^{13}$
Spline 2	-51,048	9,976	0.76×10^{-23}	1.42×10^{-31}	1.36×10^{-14}
INR (max)	0,463	0,035	1,589	1,483	1,702
Glucose (min)	-0,015	0,003	0,985	0,980	0,990
Spline 1	0,056	0,012	1,058	1,033	1,082
Spline 2	-0,174	0,043	0,840	0,772	0,915
Sodium (max)	-0,076	0,015	0,927	0,900	0,955
Spline 1	0,130	0,056	1,139	1,021	1,270
Spline 2	-0,157	0,299	0,855	0,475	1,536
Blood urea nitrogen	0,008	0,002	1,008	1,005	1,011

Interactions

Surgical * Vent onset day 1 - 2	0,082	0,142	1,085	0,822	1,434
Neurology * Vent onset day 1 - 2	-0,517	0,158	0,596	0,437	0,813
CV Surgery* Vent onset day 1 - 2	0,199	0,208	1,220	0,811	1,835
Surgical * Vent onset day 3 - 7	-0,215	0,175	0,807	0,572	1,136
Neurology * Vent onset day 3 - 7	-1,370	0,237	0,254	0,160	0,404
CV Surgery* Vent onset day 3 - 7	0,227	0,226	1,255	0,807	1,952
Surgical * Vent onset day >= 8	-0,181	0,199	0,834	0,565	1,233
Neurology * Vent onset day >= 8	-1,344	0,350	0,261	0,131	0,518
CV Surgery * Vent onset day >= 8	0,305	0,270	1,357	0,799	2,303
Surgical * thorax procedure	-0,785	0,227	0,456	0,298	0,698
CV Surgery * thorax procedure	0,603	0,217	1,828	1,111	3,007
Valve procedure* CABG	1,393	0,254	4,027	2,413	6,719
Valve procedure* aneurysm procedure	1,110	0,274	3,034	1,773	5,192
Surgical * Digestive tract procedure	0,181	0,169	1,198	0,861	1,668
Neurology * Digestive tract procedure	-0,810	0,323	0,445	0,236	0,837
CV Surgery * Digestive tract procedure	1,573	0,317	4,821	2,591	8,970
Surgical * Cranial procedure	0,215	0,493	1,240	0,472	3,256
Neurology * Cranial procedure	-1,299	0,465	0,273	0,110	0,679

Abbreviations: CABG – Coronary Artery Bypass Graft, CV Surgery – cardiovascular surgery, MV – mechanical ventilation. Spline knot locations and other data processing details are presented in section 1 of the supplementary data.

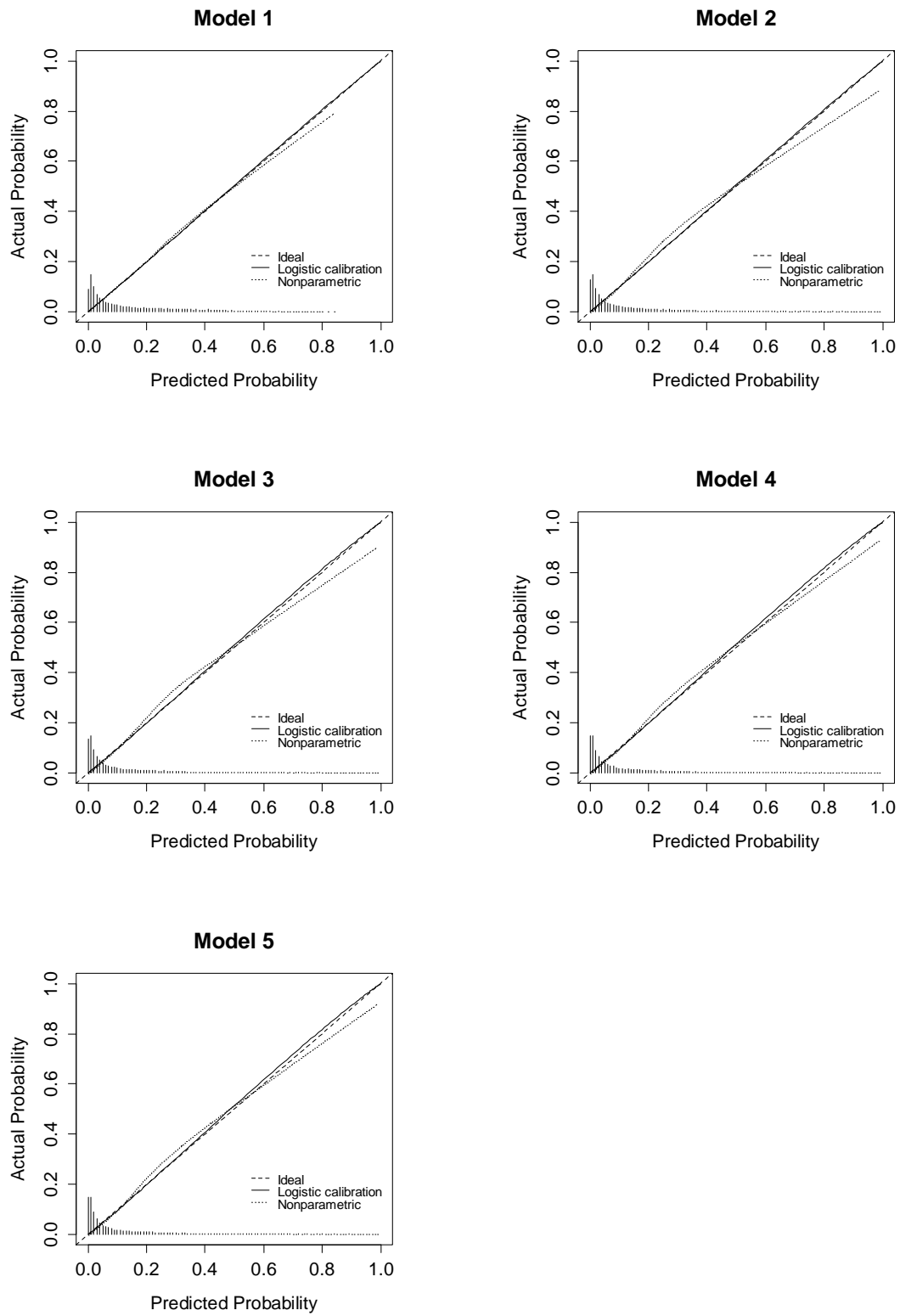**Figure S1:** Calibration plots of models developed by incremental complexity**.**

Model 1

Model 2

Model 3

Model 4

Model 5

Table S2: parameter estimates for models 1, 3, 4 and 5 predicting in-hospital mortality (for model 2, please refer to table S1).

	Model 1	Model 3	Model 4	Model 5
Intercept	-2,627	29,350	24,153	23,274
Age	0,027	0,028	0,027	0,028
Gender	-0,084	-0,076	-0,073	-0,035
Unit group (Medical = reference)				
- Surgical	-1,028	-0,448	-0,441	-0,524
- Neurology	0,139	0,913	0,989	1,085
- CV surgery	-2,358	-1,569	-1,701	-1,603
Time to MV (day of admission = reference)				
- Day 1 or 2	0,187	0,014	0,067	0,061
- Days 3-7	0,843	0,638	0,575	0,519
- >= 8 days	1,369	0,746	0,676	0,596
Any blood sample	0,312			
Procedures (>1 possible):				
Muscoskeletal	-0,717	-0,702	-0,682	-0,682
Thorax	-0,037	0,233	0,230	0,124
Lung or heart transplant	-0,889	-1,540	-1,868	-1,738
Cardiac valve	-1,210	-0,963	-0,826	-0,634
CABG	-1,587	-1,199	-1,105	-0,986
Aneurysm	-0,207	-0,543	-0,199	-0,245
Digestive tract	-0,515	-0,744	-0,741	-0,758
Cranial	0,332	1,128	1,120	0,949
Hematocrit (min)		0,021	0,023	0,022
Spline		-0,010	-0,013	-0,010
White blood cells (min)		-0,066	-0,052	-0,032
Spline 1		0,410	0,346	0,268
Spline 2		-1,056	-0,886	-0,694
Platelets (min)		-0,010	-0,009	-0,009
Spline 1		0,029	0,028	0,027
Spline 2		-0,064	-0,063	-0,062
Creatinine (max)		-0,567	-0,611	-0,507
Spline 1		16,622	16,115	15,596
Spline 2		-37,487	-36,158	-35,188
INR (max)		0,334	0,301	0,306
Glucose (min)		-0,011	-0,011	-0,012
Spline 1		0,049	0,049	0,054
Spline 2		-0,157	-0,157	-0,169
Sodium (max)		-0,067	-0,066	-0,064
Spline 1		0,105	0,119	0,117
Spline 2		-0,106	-0,200	-0,194
Blood urea nitrogen		0,008	0,009	0,008
Arterial pO2 (min)		-0,011	-0,010	-0,010
Spline 1		0,065	0,064	0,061
Spline 2		-0,138	-0,134	-0,127
Arterial pH (min)		-2,738	-2,131	-2,072
Spline 1		1,018	1,008	0,884
Spline 2		16,740	15,231	16,831

Arterial pCO2 (min)		-0,023	-0,018	-0,013
Spline 1		-0,013	-0,020	-0,026
Spline 1		0,217	0,244	0,272
Albumin (min)		-0,306	-0,287	-0,243
SGPT (max)		0,001	0,001	0,001
Total bilirubin (max)		0,069	0,068	0,068
Medication				
>2 antibiotics started			-0,13	-0,151
Antifungal (started)			0,363	0,346
Amiodarone (started)			0,256	-0,253
Nr pressors started			0,174	0,168
Anticonvulsant (started)			0,132	0,179
Steroid (started)			0,234	0,186
Vitamin K (started)			0,037	0,010
Airway (started)			-0,167	-0,130
Antipsychotic (started)			-0,073	-0,077
Comorbidities				
Congestive heart failure				-0,181
Valve disease				-0,177
Pulm circulation disorders				0,125
Peripheral vascular disease				0,118
Paralysis				-0,072
Other neurol. Disorders				0,083
Chronic lung disease				-0,128
Diabetes mellitus				-0,216
Diabetes mellitus with complications				-0,325
Hypothyroidism				-0,285
Renal failure				-0,016
Liver disease				-0,045
Chronic peptic ulcer disease				-1,662
AIDS				-0,116
Lymphoma				0,338
Metastatic cancer				0,402
Solid tumor without metastasis				-0,047
Rheumatoid arthritis/collagen vasc dis				-0,201
Coagulation deficiency				-0,007
Obesity				-0,609
Weight loss				-0,252
Fluid and electrolyte disorders				-0,076
Blood loss anemia				-0,002
Deficiency anemia				-0,282
Alcohol abuse				-0,403
Drug abuse				-0,208
Psychoses				-0,277
Depression				-0,334
Hypertension				-0,253
Interactions				
Surgical * blood sample	0,587			
Neurology * blood sample	-0,133			
CV Surgery* blood sample	0,639			
Surgical * Vent onset day 1 - 2	-0,023	0,121	0,131	0,099

Neurology * Vent onset day 1 - 2	-0,637	-0,483	-0,345	-0,335
CV Surgery* Vent onset day 1 - 2	0,273	0,330	0,333	0,303
Surgical * Vent onset day 3 - 7	-0,452	-0,220	-0,183	-0,168
Neurology * Vent onset day 3 - 7	-1,368	-1,403	-1,234	-1,273
CV Surgery* Vent onset day 3 - 7	0,265	0,285	0,300	0,356
Surgical * Vent onset day >= 8	-0,685	-0,234	-0,228	-0,185
Neurology * Vent onset day >= 8	-1,546	-1,427	-1,326	-1,385
CV Surgery * Vent onset day >= 8	0,089	0,363	0,303	0,339
Surgical * thorax procedure	-0,176	-0,748	-0,715	-0,703
CV Surgery * thorax procedure	1,161	0,684	0,658	0,698
Valve procedure*CABG procedure	2,003	1,351	1,258	1,118
Valve procedure*aneurysm	0.997	1.085		
Surgical * Digestive tract procedure	0,143	0,202	0,224	0,246
Neurology * Digestive tract procedure	-0,735	-0,666	-0,653	-0,663
CV Surgery * Digestive tract procedure	1,664	1,580	1,653	1,532
Surgical * Cranial procedure	0,754	0,061	-0,029	-0,186
Neurology * Cranial procedure	-0,825	-1,465	-1,404	-1,200
Surgical * Steroid started			0,071	0,141
Neurology* Steroid started			-1,079	-1,056
CV Surgery* Steroid started			-0,367	-0,324
Surgical * Anticonvulsant started				0,449
Neurology* Anticonvulsant started				-0,330

Table S3: Sensitivity analysis for day 30 mortality, by models of increasing complexity.

Predictor category	Model 1	Model 2	Model 3	Model 4	Model 5
Demographic	x	x	x	x	x
Unit type	x	x	x	x	x
Time to vent	x	x	x	x	x
Microbiology[a]	x	x			
Procedure codes	x	x	x	x	x
Physiology I[b]		x	x	x	x
Physiology II[b]+III[b]			x	x	x
Medication				x	x
Comorbidities					x
N independent predictors	17	36	47	56	85
Area under ROC[c]	0.840	0.872	0.877	0.880	0.884
(95% CI)	(0.833 - 0.847)	(0.866 - 0.878)	(0.871 - 0.883)	(0.874 - 0.886)	(0.879 – 0.890)
- Medical ICU	0.685	0.752	0.766	0.777	0.792
- Surgical ICU	0.741	0.818	0.826	0.830	0.834
- Neurology ICU	0.736	0.788	0.789	0.795	0.798
- CV surgery	0.760	0.839	0.845	0.846	0.858
H & L statistic	4.5	33.1	50.6	34.1	37.9
p-value H&L statistic	0.80	<0.001	<0.001	<0.001	<0.001
Brier score	0.103	0.094	0.092	0.091	0.089

Abbreviations: CV surgery – cardiovascular surgery, df – degrees of freedom, ICU – Intensive care unit, H&L statistic – Hosmer & Lemeshow statistic, ROC – Receiver Operating Characteristic.
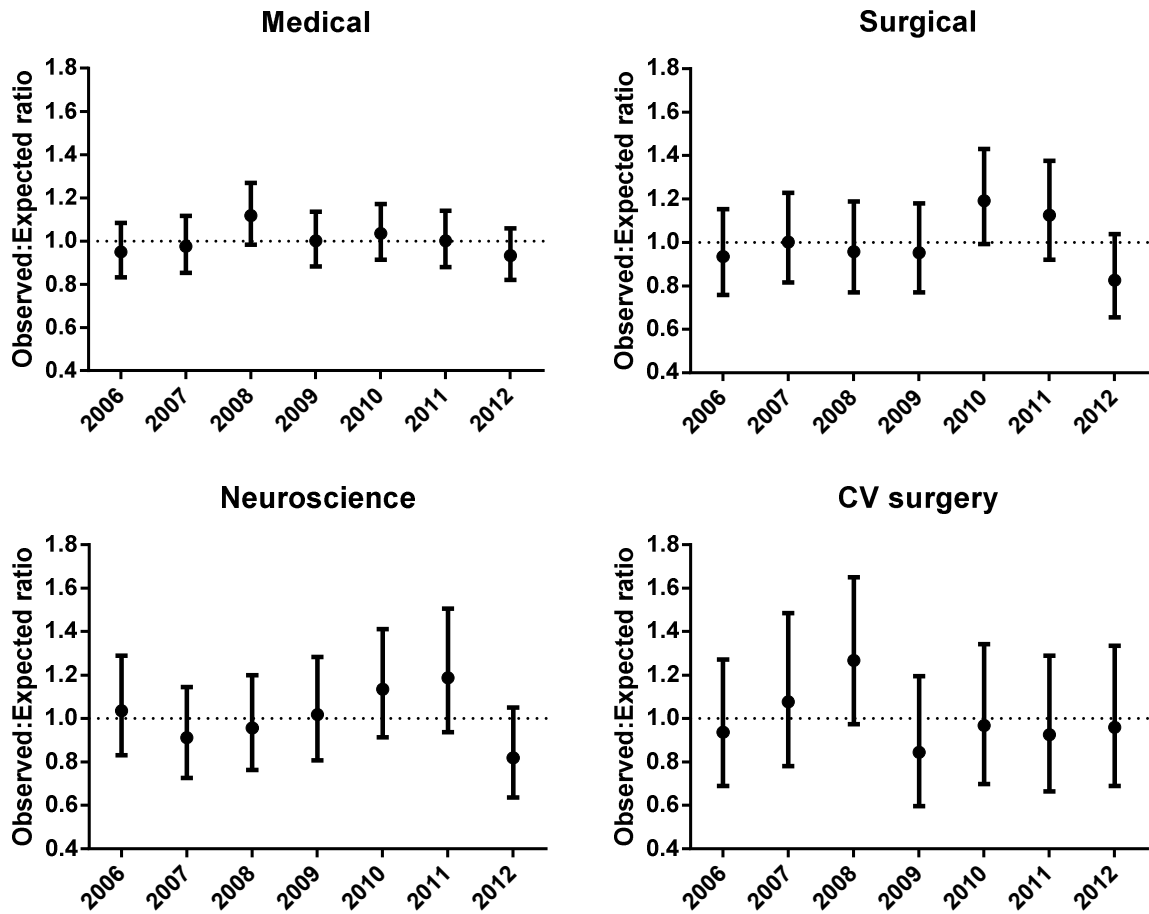
[a] Microbiology (blood culture taken) did not contribute to model performance in models 3 and up and was therefore removed. [b]: Physiology I –III, please refer to table 1 of the main text and supplementary data in section 1 for definitions. [c]: bias-corrected.

Table S4: Parameter estimates for models developed stratified by ICU type (final model).

	Medical		Surgical		Neurology		Cardiovascular surgery	
	Estim.	SE	Estim.	SE	Estim.	SE	Estim.	SE
Intercept	8.058	2.743	11,121	4,411	7,789	5,689	-2,997	10,070
Age	0,017	0.002	0,030	0,003	0,039	0,004	0,029	0,006
Female	-0,109	0.732	-0,188	0,105	-0,001	0,126	0,362	0,151
Time to MV (day of admission = reference)								
- Day 1 or 2	0,117	0.091	0,284	0,135	-0,253	0,142	0,056	0,212
- Days 3-7	0,647	0.111	0,580	0,470	-0,444	0,229	0,596	0,225
- >= 8 days	0,844	0.123	0,619	0,179	-0,250	0,370	0,768	0,276
Blood culture (obtained)	0,091	0.076	0,416	0,135	0,049	0,134	0,432	0,284
Procedures (>1 possible):								
Muscoskeletal	-0,952	0.276	-0,549	0,135	-1,364	0,474	NA	NA
Thorax	0,175	0.183	-0,348	0,135	NA	NA	0,658	0,200
Lung or heart transplant	NA	NA	-1,246	0,470	NA	NA	-1,809	0,686
Cardiac valve	NA	NA	NA	NA	NA	NA	-0,073	0,153
CABG	NA	NA	NA	NA	NA	NA	-0,246	0,149
Aneurysm	NA	NA	-0,548	0,231	NA	NA	0,222	0,208
Digestive tract	-0,658	0.131	-0,436	0,109	-1,355	0,301	0,813	0,311
Cranial	NA	NA	1,122	0,212	-0,364	0,125	NA	NA
Laboratory variables								
Hematocrit (min)	0,022	0.016	0,035	0,021	0,019	0,037	0,010	0,032
Spline	-0,041	0.020	0,000	0,028	0,003	0,040	-0,125	0,087
White blood cells (min)	-0,069	0.031	-0,145	0,044	-0,113	0,080	0,016	0,078
Spline 1	0,461	0.156	0,808	0,219	0,605	0,333	0,021	0,386
Spline 2	-1,193	0.437	-2,122	0,614	-1,515	0,892	-0,107	1,114
Platelets (min)	-0,006	0.002	-0,016	0,003	-0,016	0,005	-0,016	0,004
Spline 1	0,003	0.009	0,049	0,014	0,046	0,019	0,059	0,021
Spline 2	0,002	0.025	-0,112	0,036	-0,107	0,050	-0,134	0,062
Creatinine (max)	-1,181	0.434	-0,694	0,597	-0,332	0,675	0,532	1,366
Spline 1	25,552	6,774	18,150	9,387	12,420	11,235	15,588	19,500
Spline 2	-56,563	14,519	-40,544	20,172	-28,021	24,363	-38,247	41,317
INR (max)	0,338	0.045	0,577	0,074	0,463	0,114	0,710	0,109
Glucose (min)	-0,013	0.004	-0,020	0,005	-0,014	0,010	-0,003	0,008
Spline 1	0,043	0.017	0,080	0,024	0,066	0,035	-0,008	0,037
Spline 2	-0,127	0.062	-0,254	0,088	-0,216	0,122	0,143	0,146
Sodium (max)	-0,063	0.020	-0,098	0,032	-0,067	0,041	-0,028	0,073
Spline 1	0,129	0.080	0,225	0,114	0,097	0,139	0,004	0,208
Spline 2	-0,440	0.440	-0,561	0,612	0,058	0,723	0,558	1,022
Blood urea nitrogen	0,008	0.002	0,014	0,004	-0,001	0,006	0,008	0,006
Interactions	None	--	None	--	None	--	None	--

Abbreviations: CABG – Coronary Artery Bypass Graft, CV Surgery – cardiovascular surgery, Estim. – Estimate, MV – mechanical ventilation, SE – standard error. Note: As with all logistic regresiion models, the odds ratio can be calculated by taking the exponent of the estimated (OR = $e^{estimate}$).

Figure S2: Observed-to-expected ratios by year and ICU type.
Estimates are shown for model 2, developed stratified by ICU type.

Abbreviations: CV surgery – cardiovascular surgery.