

# SUPPLEMENTAL MATERIAL

Supplement to:

## **MCV Variation as a Predictor in Critically Ill Patients: A Retrospective Analysis of ICU Data**

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**Supplemental Table 1:** *Categorization of patient stays into disease groups based on ICD-10 codes<sup>1</sup>.*

<b>Diagnosis group</b>	<b>ICD-10 codes</b>
Diseases of the digestive system	K00-K93
Diseases of the nervous system	G00-G99
Injury, poisoning and certain other consequences of external causes	S00-S99, T00-T98
Certain infectious and parasitic diseases	A00-A99, B00-B99
Diseases of the circulatory system	I00-I99
Neoplasms	C00-C99, D00-D48
Diseases of the respiratory system	J00-J99
Diseases of the genitourinary system	N00-N99
Other	All other ICD-10 codes

<sup>1</sup>According to ICD-10 code, International Classification of Diseases codes, 10th revision, German modification.

**Supplemental Table 2:** Overview of variables, selected measurements ranges and count of excluded measurements.

	Measurement range	Excluded measurements, n (%)
<b>Demographics</b>		
Age (years)	18-130	0 (0.00)
Sex	W / M	0 (0.00)
BMI (kg/m <sup>2</sup> )	5-80	0 (0.00)
<b>Vital signs</b>		
MAP (mmHg)	10-250	2,868 (0.05)
Heart rate (/min)	10-300	1,720 (0.03)
O <sub>2</sub> saturation (%)	10-100	7,984 (0.22)
Respiratory rate (/min)	0-60	926 (0.10)
Body temperature (°C)	25-45	4,420 (0.12)
Glasgow coma scale	3-15	0 (0.00)
RASS	(-5)-4	0 (0.00)
Daily fluid balance (ml)	(-30,000)-30,000	6,890 (0.24)
<b>Laboratory parameters</b>		
Lactate, arterial/venous (mg/dl)	0-25	654 (0.05)
pH, arterial/venous	10-500	330 (0.03)
Hemoglobin (g/dl)	1-25	0 (0.00)
Thrombocytes (10 <sup>9</sup> /l)	0	0 (0.00)
Leukocytes (10 <sup>9</sup> /l)	0-150,000	0 (0.00)
C-reactive protein (mg/l)	0-2,000	0 (0.00)
Creatinine (mg/dl)	0-20	2 (0.00)
Blood urea nitrogen (mg/dl)	0-1,500	0 (0.00)
Bilirubin (mg/dl)	0-30	0 (0.00)
<b>Ventilation parameters</b>		
PaO <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> (mmHg)	10-600	2,952 (0.39)
PEEP (mb)	0-40	40 (0.00)
Tidal volume (ml)	0-2,000	4,766 (0.15)
<b>ICU scores</b>		
SAPS II	0-200	0 (0.00)
TISS-10	0-100	0 (0.00)
<b>Catecholamine dose</b>		
Epinephrine (mg/24h)	no range	0 (0.00)
Norepinephrine (mg/24h)	no range	0 (0.00)
Dobutamine (mg/24h)	no range	0 (0.00)

BMI, body mass index. MAP, mean arterial pressure. PEEP, positive end-expiratory pressure. RASS, Richmond Agitation-Sedation Scale. SAPS II, Simplified Acute Physiology Score II. TISS-10, Therapeutic Intervention Scoring System

**Supplemental Table 3:** Group comparison of clinical and laboratory parameters by MCV variation.

Parameter	FDR-p value	Effect size <i>r</i>
MCV baseline	0.055	-0.03
Max. MCV variation (%)	< 0.001	-0.51
Time in Hospital (Days)	< 0.001	-0.43
Time in ICU (Days)	< 0.001	-0.40
Total values (First 5 days)	< 0.001	-0.15

Wilcoxon rank-sum tests were performed to compare clinical and laboratory parameters between patients with *high* ( $CV > 2.5\%$ ) and *low* ( $CV \leq 2.5\%$ ) MCV variation. P-values were adjusted for multiple testing using the Benjamini–Hochberg false discovery rate (FDR). The standardized effect size *r* was calculated as  $Z / \sqrt{(n_1 + n_2)}$  to indicate the magnitude of the difference (small  $\approx 0.1$ , medium  $\approx 0.3$ , large  $\approx 0.5$ ). Negative *r* values indicate higher ranks (i.e., higher median values) in the high-variation group.

**Supplemental Table 4:** Receiver operating characteristic (ROC) analyses for different MCV-based classifications.

<b>MCV based classifications</b>	<b>AUROC</b>	<b>95% confidence interval</b>
MCV at admission (final patient cohort)	0.52	0.50-0.54
MCV coefficient of variation in the first 5days (final patient cohort)	0.61	0.59-0.62
2.5% MCV variation group in the first 5 days	0.61	0.59-0.63

**Supplemental Table 5:** Multivariable logistic regression for predictors of 2.5 % MCV variation.

<b>Variable</b>	<b>Odds Ratio (OR)</b>	<b>95% confidence interval</b>	<b>p-value (FDR adjusted)</b>
Maximum CRP	1.002	1.001-1.003	< 0.001*
Minimum hemoglobin	0.954	0.836-1.090	0.672
Maximum bilirubin	1.001	0.959-1.049	0.947
Maximum creatinine	0.968	0.902-1.044	0.672
Mean fluid balance	1.000	0.999-0.100	0.055
Maximum fluid balance	1.000	1.000-1.000	0.006*
Renal Replacement Therapy	1.230	0.890-1.710	0.599
Number of Erythrocyte Concentration	1.701	1.297-2.245	< 0.001*
Respiratory disease	2.261	1.321-3.920	0.013*
Circulatory disease	1.160	0.747-1.786	0.671
Nervous disease	1.167	0.343-4.615	0.935
Neoplasms disease	0.847	0.547-1.298	0.672
Infection disease	1.262	0.673-2.429	0.672
Trauma disease	1.172	0.724-1.896	0.672
Digestive disease	0.964	0.601-1.537	0.935
Genitourinary disease	1.389	0.669-3.024	0.672

FDR, false discovery rate. CRP, C-Reactive Protein. MAP, Mean Arterial Pressure. \* Significant

**Supplemental Table 6:** *Multivariable logistic regression analysis for predictors of in-hospital mortality.*

<b>Variable</b>	<b>Odds Ratio (OR)</b>	<b>95% confidence interval</b>	<b>p-value (FDR adjusted)</b>
Maximum CRP	1.000	0.999-1.002	0.704
Minimum hemoglobin	1.147	0.974-1.351	0.228
Maximum bilirubin	1.048	0.997-1.106	0.208
Maximum creatinine	1.080	0.991-1.176	0.211
Maximum lactate	1.179	1.114-1.252	< 0.001*
2.5% MCV variation	1.158	0.839-1.596	0.571
Mean fluid balance	1.000	1.000-1.000	< 0.001*
Maximum fluid balance	1.000	1.000-1.000	< 0.001*
Minimum MAP	0.950	0.930-0.969	< 0.001*
Minimum O <sub>2</sub> saturation	0.981	0.913-1.052	0.704
PaO <sub>2</sub> /FiO <sub>2</sub>	0.997	0.996-0.999	0.049
Maximum Ventilation use	0.998	0.996-1.001	0.550
Renal Replacement Therapy	1.041	0.735-1.472	0.857
Number of Erythrocyte Concentration	1.018	0.969-1.073	0.704
Respiratory disease	1.083	0.613-1.922	0.857
Circulatory disease	1.769	1.036-3.048	0.146
Nervous disease	2.097	0.550-7.567	0.497
Neoplasms disease	1.090	0.628-1.903	0.857
Infection disease	0.806	0.379-1.700	0.704
Trauma disease	1.024	0.578-1.824	0.935
Digestive disease	1.743	0.977-3.131	0.201
Genitourinary disease	1.523	0.627-3.728	0.571

FDR, false discovery rate. CRP, C-Reactive Protein. MAP, Mean Arterial Pressure. \* Significant

**Supplemental Table 7: Odds ratios of predictors selected by LASSO logistic regression for in-hospital mortality.**

Variable	Odds Ratio (OR)	95% confidence interval	p-value (FDR adjusted)
Mean RASS	0.751	0.702 – 0.805	<0.001*
Age	1.027	1.020 – 1.034	<0.001*
Mean SAPS	1.072	1.048 – 1.096	<0.001*
Maximum lactate	1.164	1.105 – 1.226	<0.001*
Median heartrate	1.020	1.013 – 1.027	<0.001*
Mean fluid balance	1.000	1.000 – 1.000	<0.001*
Minimum O <sub>2</sub> saturation	0.982	0.975 – 0.99	<0.001*
Maximum fluid balance	1.000	1.000 – 1.000	<0.001*
Maximum TISS	1.028	1.014 – 1.042	<0.001*
Minimum hemoglobin	0.908	0.864 – 0.954	<0.001*
Maximum SAPS	0.965	0.947 – 0.983	<0.001*
Maximum CRP	1.001	1.001 – 1.002	0.005
Mean temperature	0.739	0.613 – 0.892	0.006
Maximum respiration rate	1.018	1.006 – 1.030	0.011
Respiratory disease	0.585	0.405 – 0.844	0.013
Median tidalvolume	1.595	1.145 – 2.222	0.017
Gender	1.251	1.061 – 1.475	0.022
Maximum bilirubin	1.050	1.012 – 1.088	0.023
Maximum creatinine	1.064	1.003 – 1.129	0.099
ICU days	1.009	0.998 – 1.02	0.286
Mean PEEP	0.970	0.930 – 1.010	0.313
Maximum temperature	1.089	0.944 – 1.257	0.457
Minimum heartrate	0.995	0.988 – 1.003	0.457
Nervous disease	0.669	0.35 – 1.281	0.457
Mean thrombocytes	1.000	1.000 – 1.001	0.554
Body mass index	1.007	0.993 – 1.02	0.554
Digestive disease	1.216	0.826 – 1.789	0.554
Maximum leucocytes	1.004	0.995 – 1.013	0.619
Renal Replacement Therapy	0.899	0.686 – 1.178	0.670
Epinephrine dose in 24hours	1.028	0.957 – 1.104	0.670
Median respiration rate	0.991	0.969 – 1.015	0.681
Trauma disease	0.875	0.604 – 1.268	0.681
Infection disease	0.856	0.540 – 1.358	0.683
Minimum MAD	0.993	0.974 – 1.014	0.686
Number of Erythrocyte Concentration	1.015	0.966 – 1.067	0.710
Genitourinary disease	0.850	0.486 – 1.489	0.710
Maximum Ventilation use	1.001	0.998 – 1.003	0.711
Minimum GCS	0.983	0.915 – 1.057	0.760
PaO <sub>2</sub> /FiO <sub>2</sub>	1.000	0.999 – 1.001	0.781
Mean MAP	0.996	0.978 – 1.015	0.781
Maximum GCS	0.985	0.889 – 1.091	0.827
Mean pH	1.273	0.237 – 6.848	0.827
Neoplasms disease	1.058	0.744 – 1.504	0.827
Norepinephrine dose in 24hours	1.000	0.997 – 1.003	0.868
Circulatory disease	1.035	0.749 – 1.429	0.868
Mean GCS	0.994	0.846 – 1.168	0.942

FDR, false discovery rate. RASS, Richmond Agitation-Sedation Scale. SAPS, Simplified Acute Physiology Score, TISS, Therapeutic Intervention Scoring System. C-Reactive Protein. PEEP, Positive EndExpiratory Pressure. Mean Arterial Pressure, GCS, Glasgow Coma Scale.

Variables not selected by the penalized by LASSO logistic regression model are reported with coefficient=0:

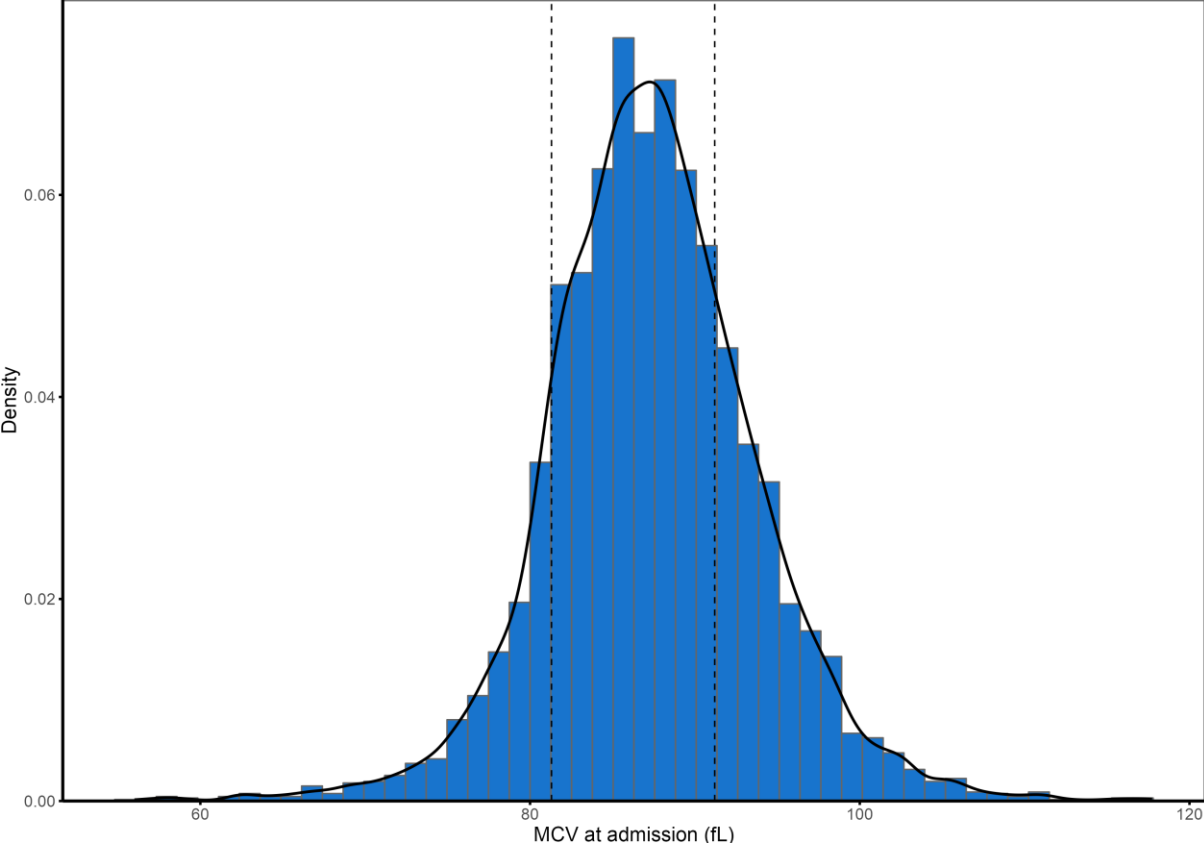
Median PEEP  
Minimum pH  
Minimum tidalvolume  
Dobutamin dose in 24h  
Mean TISS  
Minimum SAPS  
Minimum SAPS/TISS  
Diagnosis Group Other

**Supplemental Table 8: Sensitivity Analysis overview: Different patient groups.**

Analysis	Final study cohort (number of patients)	Absolute risk difference (%)	Adjusted HR (95% CI)
Main analysis	5,327	14.0	1.65 (1.46-1.87)
≥ 3 MCV values in 5 days	3,957	9.9	1.50 (1.30-1.72)
Patients with no erythrocyte transfusion	3,929	11.6	1.77 (1.52-2.07)
Patients with no hematologic disease*	5,107	13.5	1.63 (1.43-1.85)

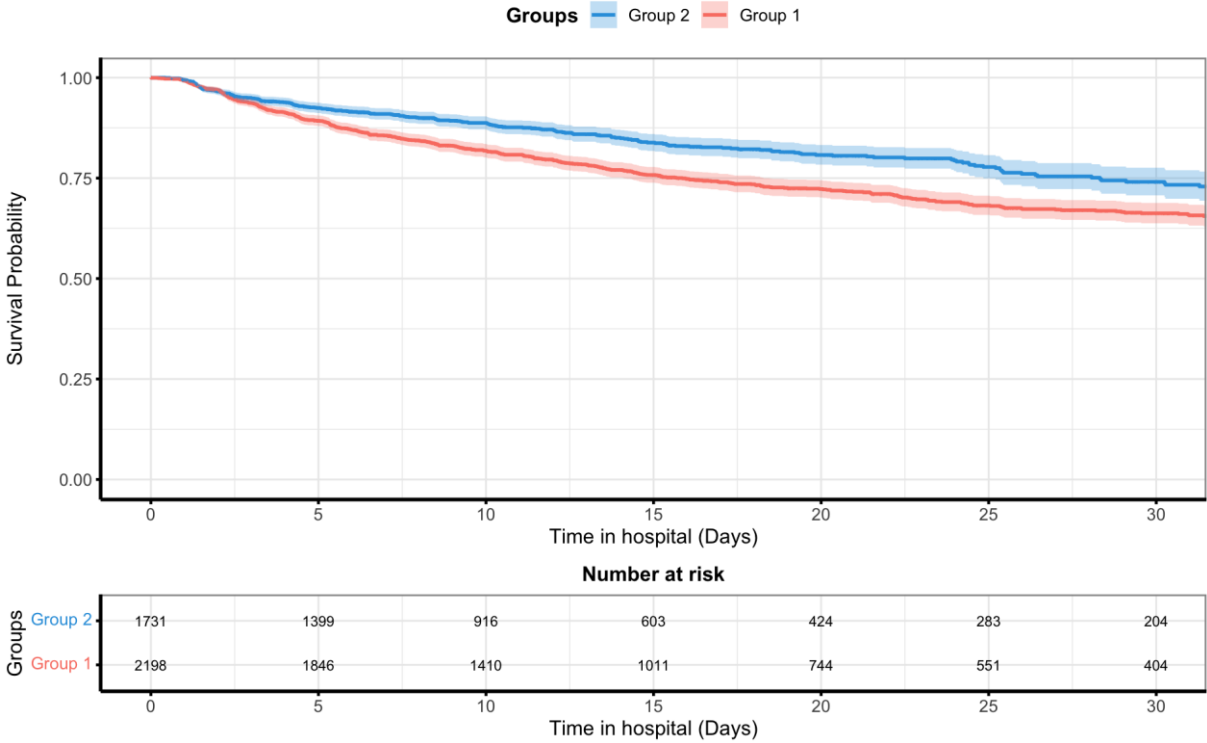
\* The following ICD-10 codes (as primary or secondary diagnoses) were used to define hematologic diseases: D46, D65-59, D51-52, C81-96. Only 279 patients were identified with these hematologic diagnoses in the study cohort.

**Supplemental Figure 1:** *Distribution of mean corpuscular volume (MCV) at ICU admission with reference range.*

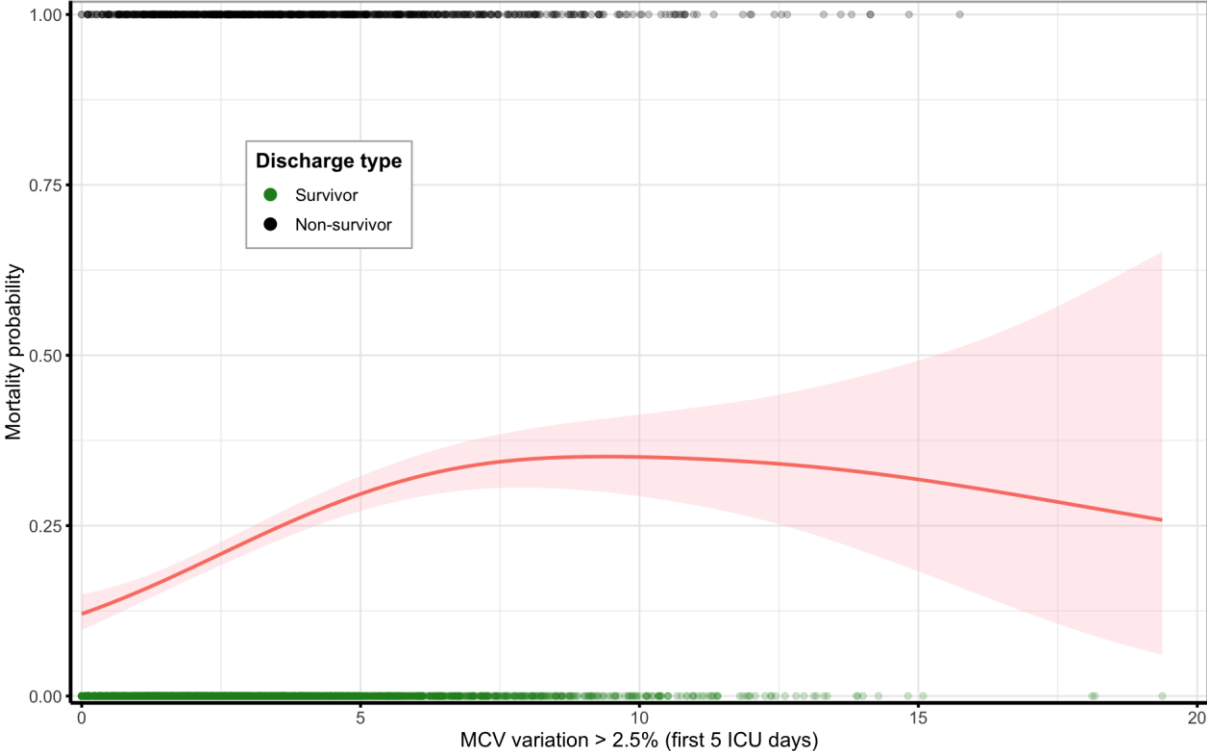


**Supplemental Figure 2:** Kaplan–Meier survival curves and GAM-based risk estimation for hospital mortality according to MCV variability in patients with no erythrocyte transfusion.

**A**

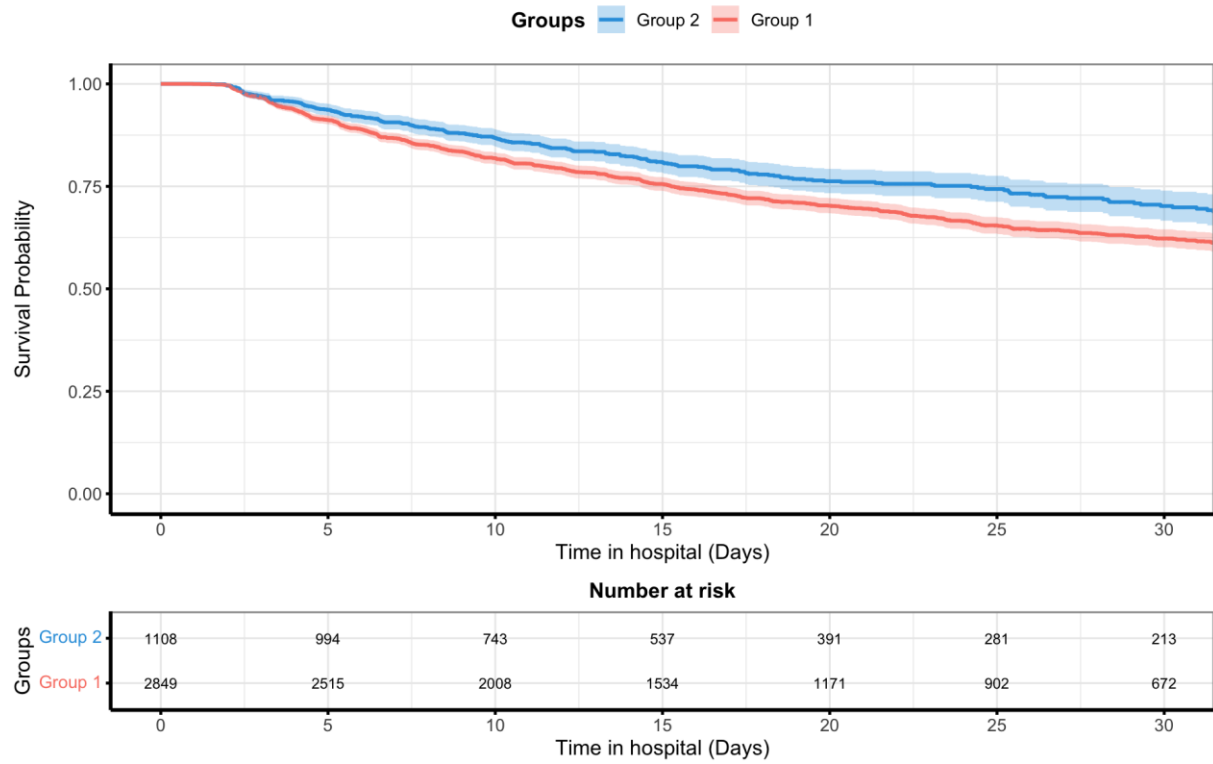


**B**



**Supplemental Figure 3:** Kaplan–Meier survival curves (A) and GAM-based risk estimation (B) for hospital mortality according to MCV variability in patients with  $\geq 3$  MCV measurements.

**A**



**B**

