

SUPPLEMENTAL MATERIAL

Red blood cell transfusion induces abnormal HIF-1 α response to cytokine storm after adult cardiac surgery

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Supplemental Table I. Association between clinical and operative variables and postoperative logHIF-1 α (N=262). Linear regression.

	Univariate analysis					Multivariate analysis	
	B	SE	β	t	P	β	P
Age	-.004	.003	-.073	-1.173	.242	NP	
Preoperative eGFR	.002	.002	.079	1.265	.207	NP	
BMI	.017	.008	.139	2.248	.025	.062	.363
Female	-.062	.088	-.044	-.708	.480	NP	
Preoperative atrial fibrillation	-.001	.085	.000	-.008	.994	NP	
Permanent	-.118	.123	-.059	-.958	.339	NP	
Paroxysmal	.345	.171	.125	2.024	.044	.038	.571
Coronary artery disease	.080	.073	.068	1.103	.271	NP	
Previous myocardial infarction	.207	.082	.155	2.538	.012	.128	.190
Recent myocardial infarction	.196	.101	.120	1.944	.053	NP	
Treatment for dyslipidemia	.173	.075	.142	2.310	.022	.132	.112
Prior PCI	.115	.170	.042	.676	.500	NP	
Prior CABG	-	-	-	-	-	NP	
Prior aortic valve surgery	-.244	.219	-.069	-1.111	.268	NP	
Prior mitral valve surgery	.113	.407	.017	.278	.781	NP	
Previous TAVR	.224	.575	.024	.390	.697	NP	
Previous percutaneous mitral valve procedure	-	-	-	-	-	NP	
Treatment for diabetes II	.058	.082	.044	.710	.478	NP	
Treatment for diabetes I	.196	.169	.072	1.158	.248	NP	
Treatment for hypertension	-.011	.089	-.008	-.127	.899	NP	
Heart failure	.072	.102	.044	.703	.482	NP	
Previous stroke	.143	.114	.077	1.251	.212	NP	
Carotid artery disease	-.565	.217	-.159	-2.604	.010	-.112	.099
Peripheral artery disease	-.066	.177	-.023	-.374	.708	NP	
Active endocarditis	.544	.406	.083	1.340	.182	NP	
Previous endocarditis	-.105	.333	-.020	-.315	.753	NP	
Hepatic cirrhosis	.056	.575	.006	.097	.923	NP	

Pulmonary artery hypertension	.056	.076	.046	.742	.459	NP	
Chronic lung disease	-.041	.113	-.023	-.367	.714	NP	
Active smoking	.170	.092	.114	1.840	.067	NP	
Ex-smoker	-.037	.070	-.033	-.534	.594	NP	
Obstructive sleep apnea	.004	.123	.002	.035	.972	NP	
CPAP mask	-.083	.163	-.031	-.507	.613	NP	
Inflammatory bowel disease	.129	.206	.039	.626	.532	NP	
Psoriatic arthropathy	.104	.237	.027	.438	.662	NP	
Skin disease	-.009	.116	-.005	-.081	.936	NP	
Seropositive rheumatoid arthritis	.183	.289	.039	.633	.527	NP	
Seronegative rheumatoid arthritis	.015	.259	.004	.057	.955	NP	
SLE/ LED	.101	.575	.011	.176	.860	NP	
Hypothyroidism	-.313	.124	-.155	-2.531	.012	-.137	.048
Hyperthyroidism	-	-	-	-	-	NP	
Malignancy	-.087	.101	-.054	-.868	.386	NP	
Active	-.344	.288	-.074	-1.192	.235	NP	
Remission	-.077	.104	-.046	-.737	.462	NP	
Poor mobility	-	-	-	-	-	NP	
Connective tissue disease	-.250	.256	-.061	-.974	.331	NP	
Chronic dialysis	.120	.286	.026	.420	.675	NP	

Operation status:

Elective	-.126	.097	-.080	-1.292	.197	NP	
Urgent	.148	.101	.090	1.462	.145	NP	
Emergency and salvage	-.092	.289	-.020	-.318	.751	NP	

Operation type:

AVR (bioprosthesis/ mechanical)	-.069	.075	-.057	-.929	.354	NP	
MPL	-.114	.130	-.054	-.876	.382	NP	
MVR	-.102	.185	-.034	-.550	.583	NP	
CABG	.130	.072	.112	1.809	.072	NP	
Only CABG	.166	.071	.145	2.355	.019	-.015	.865
Surgery on ascending aorta	-.067	.117	-.036	-.578	.564	NP	
DAVID procedure	-	-	-	-	-	NP	
Bentall procedure	-.074	.148	-.031	-.502	.616	NP	
MAZE procedure	.106	.220	.030	.485	.628	NP	
Pericardiectomy	-.474	.332	-.088	-1.428	.154	NP	
LAA closure	.108	.105	.064	1.030	.304	NP	

Other procedure	-	-	-	-	-	NP	
Indication for CABG:							
Stable	.009	.075	.007	.116	.908	NP	
UAP	-.011	.117	-.006	-.096	.924	NP	
NSTEMI	.205	.097	.130	2.119	.035	.018	.852
STEMI	.431	.406	.066	1.061	.289	NP	
Operation specifics:							
Operation length (min)	3.163E-5	.000	.010	.149	.882	NP	
Aortic cross-clamping time (min)	-.002	.001	-.088	-1.412	.159	NP	
Cardiopulmonary bypass time (min)	.000	.000	-.042	-.677	.499	NP	
Cardioplegia Antegrade	-.105	.289	-.023	-.362	.717	NP	
Cardioplegia Retrograde	-.116	.076	-.095	-1.528	.128	NP	
Endoscopic vein harvest	.297	.257	.072	1.154	.250	NP	
DHCA	-.304	.287	-.066	-1.058	.291	NP	
Delayed ventilation	-.034	.122	-.017	-.275	.783	NP	
Time in ventilator (hours)	-.001	.000	-.119	-1.924	.055	NP	
ECMO	.000	.575	.000	-.001	.999	NP	
IABP treatment	.187	.258	.045	.724	.469	NP	
Noradrenalin infusion	-.144	.332	-.027	-.433	.665	NP	
Adrenalin infusion	-.150	.136	-.069	-1.107	.269	NP	
Milrinone	-.006	.087	-.004	-.064	.949	NP	
Levosimendan	.027	.087	.019	.307	.759	NP	
Caprilon	-	-	-	-	-	NP	
Coagulation factor VIIa	-.107	.407	-.016	-.262	.794	NP	
Coagulation factor VIII	-.288	.575	-.031	-.501	.617	NP	
Coagulation factor XIII	-.163	.085	-.118	-1.917	.056	NP	
Human fibrinogen	-.481	.235	-.126	-2.047	.042	NP	
Blood products administered 12 hours							
perioperatively:							
Packed red blood cells	-.241	.085	-.190	-2.830	.005	-.151	.037
Fresh frozen plasma	-.568	.080	-.405	-7.138	.000	NP	
Platelets	-.184	.082	-.139	-2.255	.025	NP	
Intensive care unit:							
Length of stay (hours)	.003	.005	.034	.541	.589	NP	
Total fluids (12h)	-4.932E-5	.000	-.161	-2.620	.009	NP	
Drain tube bleed (12h)	-9.499E-5	.000	-.121	-1.963	.051	NP	
Diuresis (12h)	-7.984E-5	.000	-.097	-1.566	.119	NP	

AVR: aortic valve replacement; BMI: body-mass-index; CABG: coronary artery bypass grafting; CPAP: continuous positive airway pressure;
DHCA: deep hypothermic circulatory arrest; ECMO: extracorporeal membrane oxygenation; eGFR: estimated glomerular filtration rate;
IABP: intra-aortic balloon-pump; LAA: left atrial appendage; LED: lupus erythematosus disseminatus; MPL: mitral valve plasty; MVR: mitral
valve replacement; NSTEMI: non ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; SLE: systemic lupus
erythematosus; STEMI: ST-elevation myocardial infarction; TAVR: transcatheter aortic valve implantation; UAP: unstable angina pectoralis

Supplementary Table for review. Table shows multivariable logistic regression analysis of A) in-hospital adverse events; and B) 90d adverse events.

A)

		Variables in the Equation							95% C.I. for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper	
Step 1 ^a	female_male	-.395	.494	.639	1	.424	.674	.256	1.773	
	age_calculated	.032	.020	2.646	1	.104	1.033	.993	1.073	
	Log_deltaHIF	-.969	.367	6.987	1	.008	.379	.185	.778	
	treatment_for_diabetes	-.178	.397	.201	1	.654	.837	.384	1.822	
	treatment_for_hypertension	.182	.467	.153	1	.696	1.200	.481	2.994	
	heart_failure	.749	.459	2.661	1	.103	2.114	.860	5.197	
	pre.op_atrial_fibrillation	-.386	.443	.758	1	.384	.680	.285	1.621	
	coronary_artery_disease	-.200	.394	.258	1	.611	.819	.378	1.772	
	bmi	.020	.038	.275	1	.600	1.020	.947	1.099	
	preop_eGFR	.013	.009	2.282	1	.131	1.013	.996	1.031	
Constant	-5.409	2.071	6.820	1	.009	.004				
Step 2 ^a	female_male	-.385	.493	.609	1	.435	.681	.259	1.789	
	age_calculated	.033	.020	2.812	1	.094	1.033	.994	1.074	
	Log_deltaHIF	-.967	.366	6.972	1	.008	.380	.186	.779	
	treatment_for_diabetes	-.167	.396	.178	1	.673	.846	.389	1.839	
	heart_failure	.757	.458	2.725	1	.099	2.131	.868	5.235	
	pre.op_atrial_fibrillation	-.380	.443	.736	1	.391	.684	.287	1.630	
	coronary_artery_disease	-.163	.384	.180	1	.671	.850	.401	1.802	
	bmi	.021	.038	.302	1	.583	1.021	.948	1.100	
	preop_eGFR	.013	.009	2.198	1	.138	1.013	.996	1.030	
	Constant	-5.347	2.059	6.743	1	.009	.005			
Step 3 ^a	female_male	-.370	.491	.566	1	.452	.691	.264	1.809	
	age_calculated	.032	.019	2.721	1	.099	1.033	.994	1.073	
	Log_deltaHIF	-.960	.365	6.905	1	.009	.383	.187	.784	
	heart_failure	.736	.455	2.614	1	.106	2.088	.855	5.099	
	pre.op_atrial_fibrillation	-.363	.441	.676	1	.411	.696	.293	1.652	
	coronary_artery_disease	-.201	.373	.291	1	.590	.818	.394	1.698	
	bmi	.016	.036	.197	1	.657	1.016	.947	1.091	
	preop_eGFR	.013	.009	2.144	1	.143	1.013	.996	1.030	
	Constant	-5.165	1.999	6.678	1	.010	.006			
	Step 4 ^a	female_male	-.362	.491	.544	1	.461	.696	.266	1.822
age_calculated		.031	.019	2.617	1	.106	1.032	.993	1.071	
Log_deltaHIF		-.950	.364	6.816	1	.009	.387	.190	.789	
heart_failure		.724	.454	2.537	1	.111	2.062	.846	5.026	
pre.op_atrial_fibrillation		-.354	.441	.645	1	.422	.702	.296	1.665	
coronary_artery_disease		-.184	.371	.246	1	.620	.832	.402	1.721	
preop_eGFR		.012	.009	2.097	1	.148	1.013	.996	1.030	
Constant		-4.643	1.596	8.460	1	.004	.010			
Step 5 ^a		female_male	-.301	.475	.402	1	.526	.740	.292	1.878
		age_calculated	.028	.019	2.364	1	.124	1.029	.992	1.067
	Log_deltaHIF	-.965	.362	7.087	1	.008	.381	.187	.775	
	heart_failure	.737	.454	2.636	1	.104	2.090	.858	5.087	
	pre.op_atrial_fibrillation	-.319	.436	.534	1	.465	.727	.309	1.709	
	preop_eGFR	.012	.009	2.126	1	.145	1.013	.996	1.030	
	Constant	-4.616	1.596	8.364	1	.004	.010			
Step 6 ^a	age_calculated	.027	.018	2.174	1	.140	1.027	.991	1.065	
	Log_deltaHIF	-.984	.361	7.443	1	.006	.374	.184	.758	
	heart_failure	.732	.453	2.615	1	.106	2.080	.856	5.053	
	pre.op_atrial_fibrillation	-.272	.429	.403	1	.525	.761	.328	1.765	
	preop_eGFR	.014	.008	2.601	1	.107	1.014	.997	1.030	
Constant	-4.655	1.586	8.612	1	.003	.010				
Step 7 ^a	age_calculated	.025	.018	1.921	1	.166	1.025	.990	1.062	
	Log_deltaHIF	-.960	.359	7.170	1	.007	.383	.189	.773	
	heart_failure	.656	.437	2.258	1	.133	1.928	.819	4.538	
	preop_eGFR	.014	.008	2.577	1	.108	1.014	.997	1.030	
	Constant	-4.550	1.573	8.366	1	.004	.011			
Step 8 ^a	Log_deltaHIF	-.965	.359	7.220	1	.007	.381	.188	.770	
	heart_failure	.641	.436	2.167	1	.141	1.899	.809	4.458	
	preop_eGFR	.009	.008	1.330	1	.249	1.009	.994	1.024	
	Constant	-2.569	.637	16.259	1	<.001	.077			
Step 9 ^a	Log_deltaHIF	-.932	.355	6.882	1	.009	.394	.196	.790	
	heart_failure	.557	.428	1.695	1	.193	1.746	.755	4.039	
	Constant	-1.888	.209	81.837	1	<.001	.151			
Step 10 ^a	Log_deltaHIF	-.907	.354	6.578	1	.010	.404	.202	.807	
	Constant	-1.792	.190	88.872	1	<.001	.167			

a. Variable(s) entered on step 1: female_male, age_calculated, Log_deltaHIF, treatment_for_diabetes, treatment_for_hypertension, heart_failure, pre.op_atrial_fibrillation, coronary_artery_disease, bmi, preop_eGFR.

B)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)			
								Lower	Upper		
Step 1 ^a	female_male	-.177	.435	.166	1	.684	.838	.357	1.966		
	age_calculated	.028	.018	2.276	1	.131	1.028	.992	1.066		
	Log_deltaHIF	-.761	.351	4.689	1	.030	.467	.235	.930		
	treatment_for_diabetes	.009	.366	.001	1	.981	1.009	.493	2.065		
	treatment_for_hypertension	.357	.454	.620	1	.431	1.430	.587	3.481		
	heart_failure	.731	.426	2.943	1	.086	2.078	.901	4.792		
	pre.op_atrial_fibrillation	-.308	.410	.562	1	.453	.735	.329	1.643		
	coronary_artery_disease	-.269	.368	.531	1	.466	.764	.371	1.574		
	bmi	.029	.035	.703	1	.402	1.030	.961	1.103		
	preop_eGFR	.007	.008	.678	1	.410	1.007	.991	1.023		
	Constant	-4.861	1.922	6.393	1	.011	.008				
Step 2 ^a	female_male	-.178	.434	.168	1	.682	.837	.357	1.960		
	age_calculated	.028	.018	2.291	1	.130	1.028	.992	1.066		
	Log_deltaHIF	-.761	.351	4.703	1	.030	.467	.235	.929		
	treatment_for_hypertension	.358	.453	.624	1	.430	1.431	.588	3.479		
	heart_failure	.732	.424	2.984	1	.084	2.080	.906	4.775		
	pre.op_atrial_fibrillation	-.309	.408	.572	1	.450	.734	.330	1.634		
	coronary_artery_disease	-.267	.359	.552	1	.457	.766	.379	1.547		
	bmi	.030	.033	.781	1	.377	1.030	.965	1.100		
	preop_eGFR	.007	.008	.682	1	.409	1.007	.991	1.023		
	Constant	-4.869	1.888	6.651	1	.010	.008				
	Step 3 ^a	age_calculated	.026	.018	2.151	1	.142	1.027	.991	1.064	
Log_deltaHIF		-.776	.349	4.947	1	.026	.460	.232	.912		
treatment_for_hypertension		.351	.453	.600	1	.438	1.421	.584	3.454		
heart_failure		.736	.424	3.018	1	.082	2.087	.910	4.789		
pre.op_atrial_fibrillation		-.277	.401	.477	1	.490	.758	.346	1.663		
coronary_artery_disease		-.227	.346	.431	1	.512	.797	.404	1.571		
bmi		.029	.033	.758	1	.384	1.030	.964	1.099		
preop_eGFR		.007	.008	.856	1	.355	1.007	.992	1.023		
Constant		-4.874	1.884	6.694	1	.010	.008				
Step 4 ^a		age_calculated	.024	.018	1.854	1	.173	1.024	.989	1.060	
		Log_deltaHIF	-.786	.348	5.101	1	.024	.456	.231	.901	
	treatment_for_hypertension	.279	.438	.406	1	.524	1.322	.560	3.121		
	heart_failure	.750	.423	3.141	1	.076	2.118	.924	4.856		
	pre.op_atrial_fibrillation	-.244	.399	.376	1	.540	.783	.359	1.710		
	bmi	.028	.033	.695	1	.404	1.028	.963	1.098		
	preop_eGFR	.007	.008	.789	1	.374	1.007	.992	1.023		
	Constant	-4.750	1.866	6.476	1	.011	.009				
	Step 5 ^a	age_calculated	.022	.017	1.623	1	.203	1.022	.988	1.057	
		Log_deltaHIF	-.764	.346	4.871	1	.027	.466	.236	.918	
		treatment_for_hypertension	.283	.437	.417	1	.518	1.327	.563	3.127	
heart_failure		.684	.409	2.797	1	.094	1.982	.889	4.421		
bmi		.027	.033	.659	1	.417	1.027	.963	1.096		
preop_eGFR		.007	.008	.774	1	.379	1.007	.992	1.023		
Constant		-4.625	1.845	6.285	1	.012	.010				
Step 6 ^a		age_calculated	.024	.017	2.004	1	.157	1.024	.991	1.059	
		Log_deltaHIF	-.758	.345	4.824	1	.028	.469	.238	.922	
		heart_failure	.689	.409	2.847	1	.092	1.992	.895	4.438	
		bmi	.029	.033	.780	1	.377	1.030	.965	1.098	
	preop_eGFR	.007	.008	.692	1	.405	1.007	.991	1.022		
	Constant	-4.554	1.831	6.182	1	.013	.011				
	Step 7 ^a	age_calculated	.019	.015	1.465	1	.226	1.019	.988	1.050	
		Log_deltaHIF	-.740	.343	4.650	1	.031	.477	.243	.935	
		heart_failure	.631	.402	2.460	1	.117	1.879	.854	4.131	
		bmi	.028	.033	.709	1	.400	1.028	.964	1.097	
		Constant	-3.677	1.469	6.264	1	.012	.025			
Step 8 ^a		age_calculated	.018	.015	1.353	1	.245	1.018	.988	1.049	
		Log_deltaHIF	-.726	.341	4.531	1	.033	.484	.248	.944	
		heart_failure	.609	.401	2.311	1	.128	1.839	.838	4.033	
		Constant	-2.824	1.039	7.394	1	.007	.059			
		Step 9 ^a	Log_deltaHIF	-.739	.342	4.663	1	.031	.477	.244	.934
			heart_failure	.633	.400	2.507	1	.113	1.883	.860	4.124
	Constant		-1.650	.192	73.721	1	<.001	.192			
	Step 10 ^a		Log_deltaHIF	-.712	.341	4.366	1	.037	.491	.252	.957
			Constant	-1.541	.174	78.085	1	<.001	.214		

a. Variable(s) entered on step 1: female_male, age_calculated, Log_deltaHIF, treatment_for_diabetes, treatment_for_hypertension, heart_failure, pre.op_atrial_fibrillation, coronary_artery_disease, bmi, preop_eGFR.