Clinical, biochemical and genetic risk factors for 30-day and 5-year mortality in 518 adult patients subjected to cardiopulmonary bypass during cardiac surgery – the INFLACOR study

Maciej Michał Kowalik[1][✉], Romuald Lango[1], Piotr Siondalski[2], Magdalena Chmara[3], Maciej Brzeziński[2], Krzysztof Lewandowski[4], Dariusz Jagielak[2], Andrzej Klapkowski[2] and Jan Rogowski[2]

[1]Department of Cardiac Anesthesiology, Medical University of Gdańsk, Poland; [2]Department of Cardiac and Vascular Surgery, Medical University of Gdańsk, Poland; [3]Department of Biology and Genetics, Medical University of Gdańsk, Poland; [4]Department of Clinical Chemistry and Biochemistry, Medical University of Gdańsk, Poland

There is increasing evidence that genetic variability influences patients' early morbidity after cardiac surgery performed using cardiopulmonary bypass (CPB). The use of mortality as an outcome measure in cardiac surgical genetic association studies is rare. We publish the 30-day and 5-year survival analyses with focus on pre-, intra-, postoperative variables, biochemical parameters, and genetic variants in the INFLACOR (INFLAmmation in Cardiac OpeRations) cohort. In a prospectively recruited cohort of 518 adult Polish Caucasians, who underwent cardiac surgery in which CPB was used, the clinical data, biochemical parameters, IL-6, soluble ICAM-1, TNFα, soluble E-selectin, and 10 single nucleotide polymorphisms were evaluated for their association with 30-day and 5-year mortality. The 30-day mortality was associated with: pre-operative prothrombin international normalized ratio, intra-operative blood lactate, postoperative serum creatine phosphokinase, and acute kidney injury requiring renal replacement therapy (AKI-RRT) in logistic regression. Factors that determined the 5-year survival included: pre-operative NYHA class, history of peripheral artery disease and severe chronic obstructive pulmonary disease, intra-operative blood transfusion; and postoperative peripheral hypothermia, myocardial infarction, infection, and AKI-RRT in Cox regression. Serum levels of IL-6 and ICAM-1 measured three hours after the operation were associated with 30-day and 5-year mortality, respectively. The *ICAM1* rs5498 was associated with 30-day and 5-year survival with borderline significance. Different risk factors determined the early (30-day) and late (5-year) survival after adult cardiac surgery in which cardiopulmonary bypass was used. Future genetic association studies in cardiac surgical patients should account for the identified chronic and perioperative risk factors.

Table E1

Pre-, intra-, and postoperative risk factors associated with 30-day mortality in the INFLACOR study (n=518)

Variable	Survivors (n=500)	Non-survivors (n=18)	test; p-value; RR (95% CI)
Preoperative variables:			
logistic-EUROSCORE [median; IQR]	4.65 (2.59-7.21)	7.99 (3.14-12.81)	KW; 0.036
NYHA (I / II / III / IV) [%]	8 / 50 / 39 / 3	0 / 28 / 50 / 22	X^2; 0.0001
prothrombin time – INR (mean; ±SD)	1.07 ±0.15	1.14 ±0.14	A; 0.043
CKD [%]	2.9	12.1	FE; 0.02; 4.2 (1.5-12.0)
CKD-MDRD (I / II / III / IV / V) [%]	29 / 51 / 19 / 1 / 0	28 / 44 / 17 / 11 / 0	X^2; 0.025
Intraoperative variables:			
Intraoperative surgical complications	2.6	12.8	FE; 0.003; 5.0 (2.0-12.7)
CPB-time [Min] (median; IQR)	125 (100-158)	178 (128-199)	KW; 0.003
clamp-time [Min] (median; IQR)	81 (64-103)	114 (82-132)	KW; 0.008
RBCC transfusion [U] (mean; ±SD)	2.3 ±1.9	3.3 ±2.1	A; 0.031
tranexamic acid [g] (means; ±SD)	3.7 ±1.2	2.7 ±1.6	A; 0.011
PCC [%]	2.7	9.4	FE; 0.16; 3.5 (1.4-9.1)
Hipotonia [Min] (median; IQR)	5 (1-18)	15 (2-23)	KW; 0.024

Variable	Survivors (n=500)	Non-survivors (n=18)	test; p-value; RR (95% CI)
Serum lactate [mMol/dL] (median; IQR)	1.7 (1.4-2.1)	2.4 (2.0-3.2)	KW; 0.0000
Serum glucose [mg/dL] (median; IQR)	150 (131-171)	177 (148-193)	KW; 0.009
Use of adrenaline infusion [%]	2.6	27.8	FE; 0.0002; 10.7 (4.3-26.8)
Use of dobutamine infusion [%]	2.4	6.6	X^2; 0.021; 2.8 (1.1-6.9)
Highest dobutamine dose used [µg/kg/Min] (mean; ±SD)	6.5 ±5.3	11.3 ±7.5	A; 0.019
Postoperative variables:			
Infection [%]	1.8	14.7	FE; 0.00002; 8.3 (3.4-20.2)
New antibiotic treatment [%]	1.3	5.1	FE; 0.027; 3.8 (1.2-13.1)
Positive bacterial culture [%]	2.1	25.8	FE; 0.000002; 12.6 (5.3-29.6)
CXR lung parenchyma opacities [%]	2.3	7.1	FE; 0.02; 3.1 (1.2-7.6)
Postoperative myocardial infarction [%]	2.9	9.3	FE; 0.05; 3.2 (1.1-9.2)
Postoperative psychosis [%]	2.2	12.1	FE; 0.0007; 5.5 (2.2-13.4)
Acute kidney injury [%]	1.7	9.6	FE; 0.0003; 5.5 (2.2-13.9)
Renal replacement therapy [%]	2.2	53.9	FE; 0.00000003; 24.7 (11.4-53.5)
Intra-aortic balloon pump [%]	2.8	33.3	FE; 0.0004; 12.0 (4.6-31.2)
Resternotomy / pneumothorax	2.8	9.3	FE; 0.03; 3.3 (1.2-8.9)
IL-6 [pG/mL] (median; IQR)	162 (67-366)	368 (80-1777)	KW; 0.038

Variable	Survivors (n=500)	Non-survivors (n=18)	test; *p*-value; RR (95% CI)
Length of stay in ICU [hours] (median; IQR)	41 (21-68)	103 (24-258)	KW; 0.005
RBCC transfusion [U] (mean; ±SD)	1.0 ±1.3	1.7 ±1.4	A; 0.03
FFP transfusion [U] (mean; ±SD)	1.8 ±1.9	3.0 ±2.2	A; 0.01
Chest tube drainage [mL/hour] (mean; ±SD)	16.5 ±2.7	14.8 ±3.3	A; 0.008
Highest finger tip day 1. temperature [C^0] (median; IQR)	36.6 (35.9-37.1)	36.1 (35.5-36.5)	KW; 0.007
APACHE-III on day 1. (median; IQR)	33 (24-41)	42 (38-64)	KW; 0.0003
SAPS-II on day 1. (median; IQR)	22 (18-27)	32 (26-38)	KW; 0.0001
Mechanical ventilation [hours] (median; IQR)	11.6 (8.4-17.5)	48.5 (11-148)	KW; 0.001
Prothrombin time INR (median; IQR)	1.10 (1.06-1.16)	1.16 (1.10-1.25)	KW; 0.02
Creatine phosphokinase in serum [IU/mL] (median; IQR)	638 (415-1094)	1462 (1046-1772)	KW; 0.004
Creatine phosphokinase MB-fraction in serum [IU/mL] (median; IQR)	22.3 (14.4-39.2)	39.5 (24.3-56.9)	KW; 0.007

Table E2

Pre-, intra-, and postoperative risk factors associated with 5-year mortality in the INFLACOR study (n=518)

Variable	Survivors (n=398)	Non-survivors (n=120)	test; *p*-value; RR (95% CI)
Preoperative variables:			
Age [years] (median; IQR)	65 (58-73)	69 (62-77)	KW; 0.0000
logistic-EUROSCORE [median; IQR]	4.3 (2.3-6.8)	6.4 (4.0-9.2)	KW; 0.0000
NYHA (I / II / III / IV) [%]	8 / 53 / 36 / 3	5 / 38 / 52 / 6	X^2; 0.002
Coronary artery disease [%]	41.7	56.7	0.0034
Myocardial infarction >90 days before operation [%]	9.0	20.0	0.0009
CCS (1 / 2 / 3 / 4) [%]	44 / 33 / 22 / 1	31 / 33 / 35 / 2	X^2; 0.013
Chronic atrial fibrillation [%]	18.6	30.8	0.0046
Left ventricle ejection fraction [%] (mean; ±SD)	56 ±11	51 ±13	A; 0.0005
CKD [%]	4.5	13.3	0.00013
CKD-MDRD (I / II / III / IV / V) [%]	31 / 51 / 18 / 1 / 0	23 / 50 / 23 / 4 / 1	X^2; 0.009
Haemoglobin in blood [g/dL] (median; IQR)	13.7 (12.7-14.8)	13.3 (11.9-14.7)	KW; 0.04
Creatinine in serum [mg/dL] (median; IQR)	0.89 (0.76-1.07)	0.98 (0.82-1.2)	KW; 0.0014

Variable	Survivors (n=398)	Non-survivors (n=120)	test; *p*-value; RR (95% CI)
Glomerular filtration rate [mL/Min] (mean/median; IQR)	57/60 (59-60)	54/60 (54-60)	KW; 0.001
Blood urea nitrogen [mg/dL] (median; IQR)	18.0 (14.6-21.8)	20.0 (16.7-25.8)	KW; 0.0002
Glomerular filtration rate – MDRD [mL/Min] (mean/median; IQR)	81 (65-94)	74 (57-89)	KW; 0.001
Glomerular filtration rate – CG [mL/Min] (mean/median; IQR)	81 (66-103)	72 (53-92)	KW; 0.0005
Loop-diuretic treatment [%]	27.1	40.8	0.0024
Spironol treatment [%]	18.6	31.7	0.0023
Chronic obstructive pulmonary disease	5.3	11.7	0.014
Treatment with at least two inhaled drugs [%]	1.8	6.7	0.0028
Peripheral artery sclerosis [%]	5.0	12.5	0.0038
Intraoperative variables:			
Operation-time [Min] (mean; ±SD)	4.4 ±1.2	4.7±1.3	A; 0.012
CPB-time [Min] (mean; ±SD)	132 ±50	144 ±56	A; 0.028
Midazolam (n=114 / n=38) [mg/kg] (mean; ±SD)	0.18 ±0.18	0.25 ±0.22	A; 0.049
RBCC transfusion [U] (median; IQR)	2 (1.5-3.5)	3 (1.5-4.5)	KW: 0.0011
Platelets concentrate transfusion [U] (means; ±SD)	1.2 ±2.7	1.8 ±3.1	A; 0.04
PCC transfusion [%]	10.6	18.3	0.016

Variable	Survivors (n=398)	Non-survivors (n=120)	test; *p*-value; RR (95% CI)
Serum lactate [mMol/dL] (median; IQR)	1.7 (1.4-2.1)	1.9 (1.7-2.5)	KW: 0.0025
Base excess [mMol/dL] (mean; ±SD)	-3.7 (±2.2)	-4.2 (±2.4)	A; 0.027
Use of adrenaline infusion [%]	2.5	6.7	0.015
Use of dobutamine infusion [%]	22.4	40.0	0.00008
Highest dobutamine dose used [µg/kg/Min] (median; IQR)	5.2 (3.5-6.7)	6.5 (4.7-9.8)	KW; 0.01
Intra-operative surgical complications [%]	7.5	14.2	0.016
Postoperative variables:			
Length of stay in ICU [hours] (mean; ±SD)	55 ±93	79 ±103	A; 0.02
Stroke [%]	1.5	4.2	LR; 0.04
Sepsis [%]	10.3	22.5	LR; 0.0002
Antibiotic therapy [%]	53.8	65.8	LR; 0.0128
Positive microbial culture [%}	3.8	13.3	LR; 0.00002
Myocardial infarction [%]	5.8	16.7	LR; 0.0001
Delirium	10.3	20.8	LR; 0.001
Acute kidney injury [%]	18.3	35.0	LR; 0.00005
Acute kidney injury with renal replacement therapy [%]	0.8	8.3	LR; 0.00000

Variable	Survivors (n=398)	Non-survivors (n=120)	test; *p*-value; RR (95% CI)
Platelets concentrate transfusion [U] (mean/median; IQR)	1.2/0 (0-1)	1.9/0 (0-4)	KW; 0.025
Chest tube drainage [mL/hour] (mean; ±SD)	16.6 ±2.7	16.0 ±3.0	A; 0.04
Highest fingertip day 1. temperature [C^0] (median; IQR)	36.6 (36.1-37.1)	36.4 (35.7-37.0)	KW; 0.005
APACHE-III on day 1. (median; IQR)	32 (24-39)	36 (28-47)	KW; 0.0000
SAPS-II on day 1. (median; IQR)	22 (18-27)	25 (20-30)	KW; 0.0001
Mechanical ventilation [hours] (median; IQR)	11.3 (8.3-17.0)	14.6 (8.6-19.9)	KW; 0.002
Creatinine in serum on 1st postop day [mg/dL] (median; IQR)	0.88 (0.75-1.10)	0.99 (0.81-1.35)	KW; 0.0004
Creatine phosphokinase in serum [IU/mL] (median; IQR)	631 (410-1045)	779 (478-1532)	KW; 0.01
Creatine phosphokinase MB-fraction in serum [IU/mL] (median; IQR)	21.2 (13.2-37.5)	27.3 (19.4-48.4)	KW; 0.0001
Troponin I in serum [IU/mL] (median; IQR)	6.6 (3.9-13.5)	11.7 (5.7-22.0)	KW; 0.0004
Glomerular filtration rate – CG [mL/Min] (mean; ±SD)	85 ±31	73 ±40	A; 0.0002
Glomerular filtration rate – MDRD [mL/Min] (mean/median; IQR)	81 ±26	71 ±28	A; 0.0002
ICAM-1 [pg/μL] (median; IQR)	34.1 (26.6-44.3)	37.8 (29.6-49.0)	KW; 0.016