Supplemental Material

Methods

Patient treatment

VA-ECMO was utilized to stabilize hemodynamics, enable transfer from a referral hospital, perform extracorporeal-cardiopulmonary resuscitation, or to treat biventricular failure. Implantation of an Impella was performed in patients with CS with left-ventricular (LV) failure or LV distension on VA-ECMO. Impella implantation, positioning and anticoagulation were performed as previously described.[1] Management of sympathomimetic inotropic and vasopressor agent was performed at the estimation of the clinician in charge targeting decrease of drugs account, dosis and duration to minimize the risk of mediated end-organ failure. Target blood pressure was defined as MAP ≥65 mmHg and SBP ≥80 mmHg or individualized determined by the treating clinician. However, despite our institutional standards, we thus cannot exclude bias. Appropriateness of end-organ perfusion was verified by considering markers of systemic perfusion: arterial lactate, central or mixed venous oxygen saturation, urine output, and if a pulmonary artery catheter was considered: cardiac output, pulmonary capillary wedge pressure, and peripheral vascular resistance.

A left ventricular endomyocardial biopsy (EMB) was obtained if the procedure was considered safe by the interventional cardiologist at the time of Impella implantation.

Clinical parameters, complications, and demographic characteristics were continuously documented in a standard patient file and data monitoring system. Patients were followed-up until 30 days. Records were extracted from the electronic hospital patient data management system. In case of discharge before 30 days after admission consecutive outpatient visits and/or chart review were performed. No patient was lost to follow-up.,

Propensity score matching

To minimize confounding bias due to the non-randomized nature of the investigation, to yield a balanced distribution of baseline characteristics and to estimate effects of dual circulatory support with Impella and VA-ECMO in patients with Influenza-related myocarditis and rCS a propensity score matching was performed to patients with rCS due to acute myocardial infarction (AMI-rCS group) and to patients with non-ischemic cardiomyopathy complicated by rCS (DCM-rCS group). Propensity scores were estimated using multivariable logistic regression modelling accounting for variables related to the outcome [2]: biventricular failure at baseline, out-of-hospital cardiac arrest with initial shockable rhythm and duration from shock to first device [hours]. Cases of influenza related myocarditis and control groups were matched stepwise on the logit of the estimated propensity score (1:2 propensity score matching) using a nearest neighbor model using calipers width equal to 0.15. In our study a lower caliper width was used in order to maximize correct matching and to reduce bias.

To validate the method and perform a sensitivity analysis of the propensity score matching, the primary outcome (30-day mortality) was reanalyzed using the entire (unmatched) cohort (Supplemental Fig S1)

Review of the literature

Literature review between 2013 and 2019 was performed using PubMed search engine and the following criteria: infuenza, myocarditis, mechanical circulatory support. Original research articles, Case reports, and case series handling with adult patients with verified influenza virus infection, proven or suspected myocarditis, cardiogenic shock and MCS using VA-ECMO and/or Impella were eligible. Manuscripts with limited clinical information were excluded. Parameters were selected as follows: Influenza virus type, patients` characteristics (i.a. pre-existing conditions, vaccination status, occurence of cardiac arrest), use of inotropes/vasopressors, mechanical ventilation, lactate levels, complications (i.a. renal replacement therapy, pericardial effusion, pneumonia), type of MCS, intention to treat, outcome data.

Supplemental Table S1: Patient characteristics

	Patients with Influenza related myocarditis complicated by cardiogenic shock n= 7	Patients with myocardial infarction complicated by cardiogenic shock n= 14	P Influenza-rCS vs AMI-rCS	Patients with non-ischemic cardiomyopathy complicated by cardiogenic shock n=14	P Influenza-rCS vs DCM-rCS
height [cm]	175±6	172±12	ns	176±9	ns
weight [kg]	81±14	86±12	ns	87±18	ns
pre-existing disease					
stroke	0	1 (7%)	ns	1 (7%)	ns
PAD	0	1 (7%)	ns	1 (7%)	ns
myocardial infarction	0	14 (100%)		0	
STEMI	0	11 (79%)		0	
NSTEMI	0	3 (21%)		0	
cardiomyopathy					
myocarditis	7 (100%)	0		0	
dilative		0		14 (100%)	
extrahospital thrombolysis	0	4 (29%)	ns	2 (14%)	ns

AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, NSTEMI- Non-ST-elevation myocardial infarction, PAD- Peripheral artery disease, STEMI- ST-elevation myocardial infarction

Supplemental Table S2: Intensive care and mechanical circulatory support

		Patients with Influenza related myocarditis complicated by cardiogenic shock n= 7	Patients with myocardial infarction complicated by cardiogenic shock n= 14	P Influenza-rCS vs AMI-rCS	Patients with non-ischemic cardiomyopathy complicated by cardiogenic shock n=14	P Influenza-rCS vs DCM-rCS
in-hospital stay [days]		3 [1-16]	18 [1-25]	ns	14 [5-36]	***0.025***
mechanical ventilation		7 (100%)	14 (100%)	ns	14 (100%)	ns
coronary angiography		7 (100%)	14 (100%)	ns	14 (100%)	ns
PCI performed		1 (14%)	14 (100%)	***0.005***	0	ns
type of Impella				ns		ns
	2.5	1 (14%)	2 (14%)		2 (14%)	
	CP	6 (86%)	12 (86%)		12 (86%)	
shock to Impella-insertion-time				ns		ns
	<6 hours	2 (29%)	9 (64%)		4 (29%)	
	6-12 hours	1 (14%)	0		1 (7%)	
	12-24 hours	1 (14%)	1 (7%)		0)	
	>24 hours	2 (29%)	4 (29%)		9 (64%)	
duration of Impella-support [hours]		28 [11- 326]	129 [28-203]	ns	80 [64-147]	ns
ECMO support		7 (100%)	14 (100%)	ns	14 (100%)	ns
	duration of ECMO support [hours]	43 [14-312]	196 [23-331]	ns	114 [94-166]	ns
	duration shock to	20 [2-32]	10 [4-23]	ns	20 [3-30]	ns

	ECMO [hours]					

AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, ECMO- Extracorporeal membrane oxygenation, Influenza-rCS- Patients with influenza associated refractory cardiogenic shock, PCI- Percutaneous coronary intervention, VA- Veno-arterial

Supplemental Table S3: Outcome

		Patients with Influenza related myocarditis complicating cardiogenic shock n= 7	Patients with myocardial infarction complicated by cardiogenic shock n= 14	P Influenza-rCS vs AMI-rCS	Patients with non-ischemic cardiomyopathy complicated by cardiogenic shock n=14	P Influenza-rCS vs DCM-rCS
hemolysis		1 (14%)	4 (29%)	ns	10 (71%)	***0.013***
anoxic brain damage		1 (14%)	2 (14%)	ns	1 (7%)	ns
TIMI bleeding				ns		ns
	none	2 (29%)	6 (43%)		8 (57%)	
	minimal	3 (43%)	1 (7%)		4 (29%)	
	minor	2 (29%)	7 (50%)		2 (14%)	
	major	0	0		0	

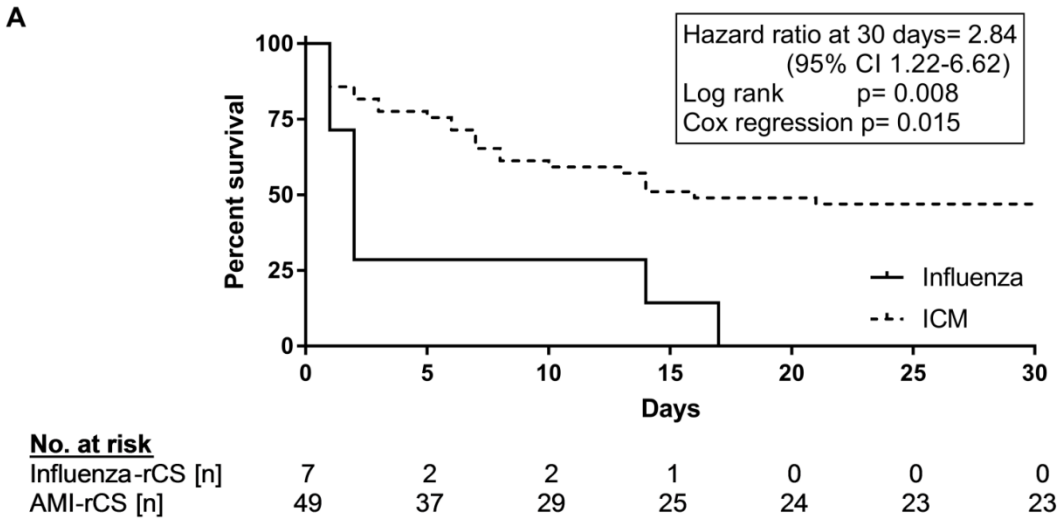
AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, Influenza-rCS- Patients with influenza associated refractory cardiogenic shock

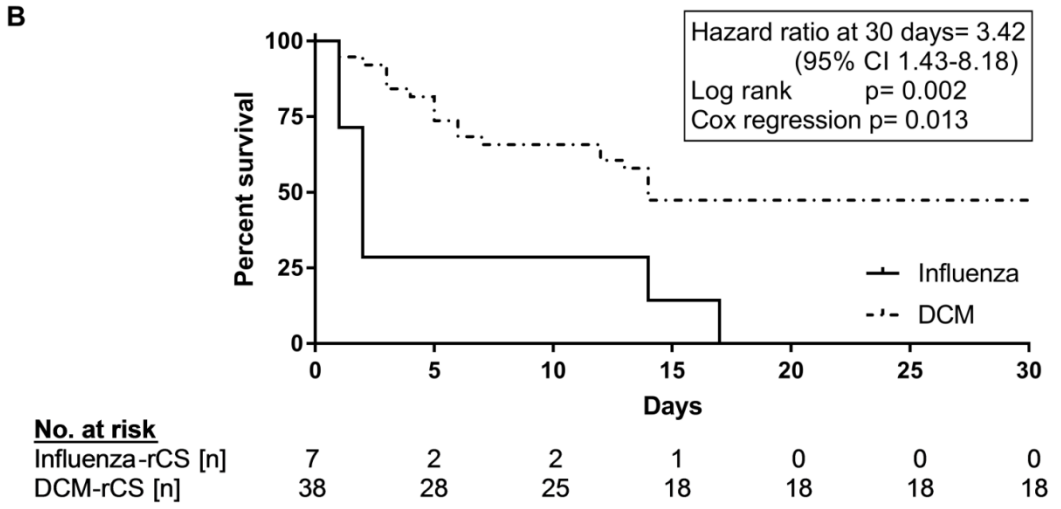
Supplemental Table S4: Summary of case reports (2013-2019) targeting adult patients with influenza-related cardiogenic shock requiring mechanical circulatory support (VA-ECMO and/or Impella) and additional administration of inotropes/vasopressors.

Parameter	**Larsen TR et al.[3]**	**Taremi M et al. [4]**	**Hamoudi A et al. [5]**	**Ciabatti M et al. [6]**	**Marchetti L et al.[7]**	**Siskin M et al. [8]**	**Hekimian G et al. [9]**	**Hekimian G et al. [9]**	**Hekimian G et al. [9]**	**Hekimian G et al. [9]**
virus (RT-PCR)	A (H1N1)	B	A (H1N1)	B	B	B	B	B	B	B
age [y]	41	52	25	66	44	22	28	35	43	39
sex	F	F	F	M	M	F	F	F	F	M
pre-existing conditions	N	N	Nicotine	N	Nicotine, Non-Hodgkin lymphoma	N	Ectopic pregnancy	N	Multiple sclerosis	N
vaccination	NN	NN	NN	NN	N	NN	NN	NN	NN	NN
transferred in CS	N	Y	Y	N	Y	N	N	N	Y	N
beginning of flu-like symptoms	-4d	-6d	-7d	-2d	-2d	-14d	-3d	-3d	-5d	-5d
Mechanical ventilation	Y	Y	NN	NN	Y	NN	NN	NN	NN	NN
peak lactate [mmol/L]	8.8	8.2	NN	11	NN	4	9.8	10	3.7	14.4
inotropes/vasopressors	Y (n=1, NE)	Y (n=1, NE)	Y (n=2, NE, D)	Y (n=2, NE, D)	Y (n=2, NE, D)	Y (n=1, D)	Y (n=1, D)	Y (n=2, E, D)	Y (n=1, D)	Y (n=1, D)
LVEF [%]	30	10	35	10	15	10	20	10	10	10
PE	Y	N	N	Y	Y	Y	Y	Y	Y	Y
MCS	IABP/ Impella 2.5	VA-ECMO	VA-ECMO	IABP + VA-ECMO	VA-ECMO/ IABP	Impella	VA-ECMO	IABP + VA-ECMO	VA-ECMO	VA-ECMO
cardiac arrest	Y	N	N	Y	N	N	N	N	N	N
biventricular failure	NN	N	N	N	Y	N	NN	Y	NN	Y
ARDS	N	N	N	N	N	N	N	N	N	N
secondary pneumonia	N	N	N	N	N	N	N	N	N	N
RRT	Y	N	N	Y	N	N	N	Y	N	Y
bridge to	Destination	Recovery	Destination	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery
in-hospital survival	N	Y	N	Y	Y	Y	Y	Y	Y	Y

ARDS- acute respiratory distress syndrome, CS- cardiogenic shock, D- dobutamine, E-epinephrine, F- female, IABP- intra-aortic balloon pump, LVEF- left ventricular ejection fraction, M- male, MCS- mechanical circulatory support, N- no, NE- norepinephrine NN- not reported, PE- pericardial effusion, RRT- renal replacement therapy, VA-ECMO- venou-arterial extracorporeal membrane oxygenation, Y- yes

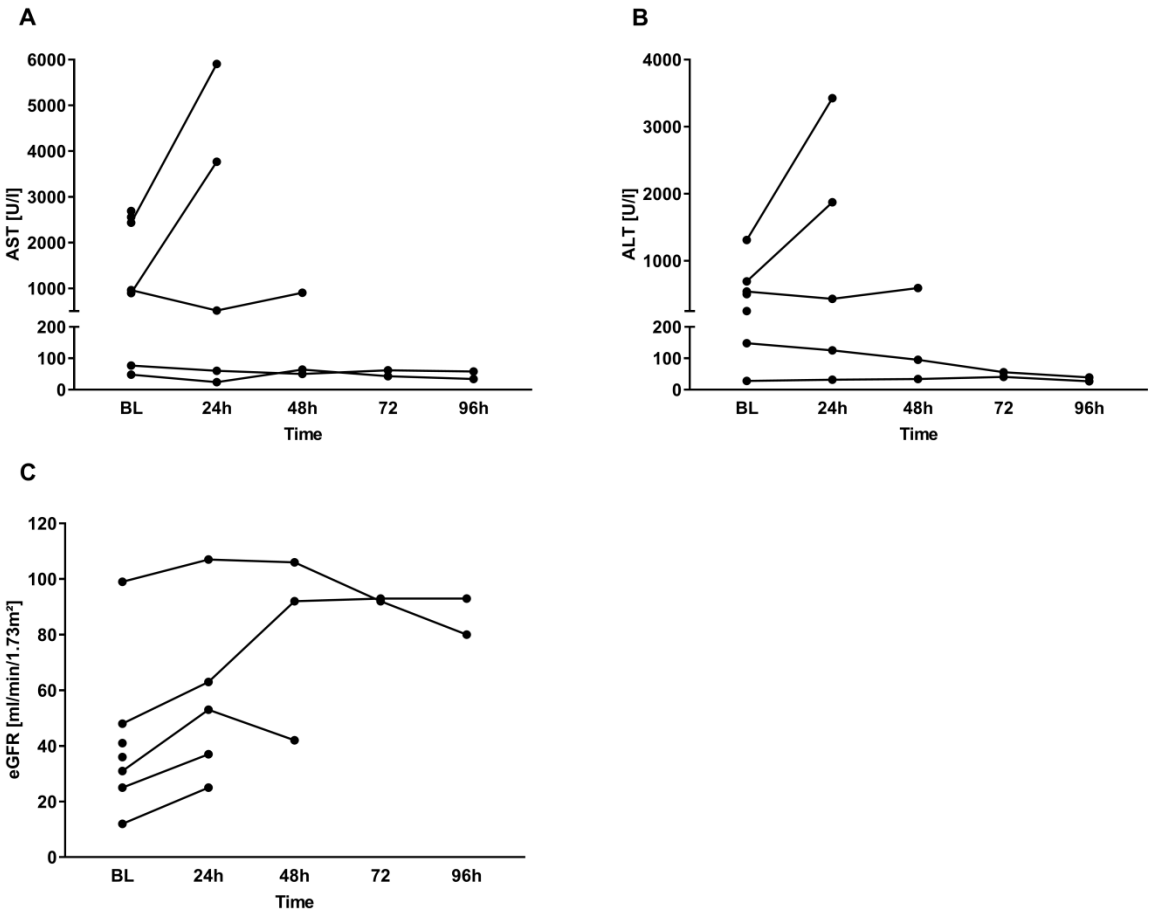
<u>Supplemental Figure S1:</u> Kaplan-Meier curves comparing 30 day survival between the Influenza group and the unmatched groups of patients with AMI related rCS (A) and patients with DCM related rCS (B)





AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, CI- Confidence interval, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, Influenza-rCS- Patients with influenza associated refractory cardiogenic shock

<u>Supplemental Figure S2:</u> Course of AST, ALT and eGFR in patients with influenza associated myocarditis related refractory cardiogenic shock



A: AST over time, **B:** ALT over time, **C:** eGFR over time

ALT- Alanine aminotransferase, AST- Aspartate aminotransferase, BL- Baseline, eGFR- estimated glomerular filtration rate

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