Supplementary materials

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Association between early oxiris hemoadsorption and survival in critically ill COVID-19 patients: a single-center risk-set-matched cohort study

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Content

Annex 1: clinical indications and technical specifications for oXiris hemoadsorption therapy

Item	Specification
Clinical indications: patients met at least one of the following criteria	
Respiratory status	Severe ARDS (PaO_2/FiO_2 ratio < 100) or progressive respiratory failure (PaO_2/FiO_2 ratio < 300) despite standard anti-inflammatory therapy.
Hemodynamics	Septic shock or hemodynamic instability requiring vasopressors to maintain a mean arterial pressure ≥ 65 mmHg.
Multiorgan dysfunction	An acute increase in total SOFA score of ≥ 2 points.
Technical specifications (followed the Asia-Pacific expert consensus on extracorporeal blood purification for sepsis/COVID-19)	
System and filter	Prismaflex system with oXiris filter set (AN69ST membrane surface treated with heparin and polyethyleneimine [PEI]).
Mode	CVVH or CVVHDF.
Treatment dose	Effluent dose: 25–35 mL/kg/h.
Blood flow rate	150–200 mL/min.
Anticoagulation	Individualised: regional citrate anticoagulation or systemic heparinization, monitored by aPTT or ACT.

Abbreviations: ARDS, acute respiratory distress syndrome; SOFA, Sequential Organ Failure Assessment; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; PEI, polyethyleneimine; aPTT, activated partial thromboplastin time; ACT, activated clotting time.

Annex 2: sensitivity analyses of the association between early oXiris hemoadsorption and 28-day mortality

Analysis	Analytic sample	Early oXiris	Control	Effect estimate (95% CI)	p-value
Primary analysis (calliper 0.2 SD)	248 pairs	80/248 (32.3%)	83/248 (33.5%)	HR 0.86 (0.59–1.26)	0.45
SA1: Stricter caliper (0.1 SD)	238 pairs	81/238 (34.0%)	80/238 (33.6%)	—	1.000
SA2: Wider caliper (0.25 SD)	248 pairs	80/248 (32.3%)	75/248 (30.2%)	—	0.685
SA3: Additional exact matching on CRP and IL-6 quartiles	38 pairs	13/38 (34.2%)	11/38 (28.9%)	—	0.752
SA4: IPTW (ATT), day-3 landmark complete-case cohort	n = 769	29.5%*	26.0%*	OR 1.19 (0.81–1.75)	0.364

Abbreviations: SA, sensitivity analysis; SD, standard deviation; CRP, C-reactive protein; IL-6, interleukin-6; IPTW, inverse probability of treatment weighting; ATT, average treatment effect in the treated; HR, hazard ratio; OR, odds ratio; CI, confidence interval. The primary analysis used sequential risk-set propensity score matching with a caliper width of 0.2 SD of the logit propensity score, and the treatment effect was estimated using a stratified Cox proportional hazards model. SA1–SA3 were based on alternative matching specifications; p-values for these matched analyses were derived from conditional logistic regression. SA4 used a day-3 landmark complete-case cohort with IPTW for the ATT estimand, and the effect estimate was derived from weighted logistic regression. *Weighted event proportions estimated in the IPTW pseudo-population. "—" indicates that no model-based effect estimate was reported for that analysis.

Annex 3: baseline characteristics and clinical outcomes in the narrower-calliper matched cohort (0.1 SD of the logit propensity score)

Panel A. Baseline and index-day characteristics

Characteristic	Early oXiris group (n = 238)	Control group (n = 238)	P-value	SMD
Demographics and comorbidities				
Age (years), mean ± SD	59.2 ± 19.6	59.2 ± 20.0	0.979	0.002
Male, n (%)	129 (54.2%)	130 (54.6%)	1	0.008
Any comorbidity, n (%)	183 (76.9%)	184 (77.3%)	1	0.010

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Characteristic	Early oXiris group (n = 238)	Control group (n = 238)	P-value	SMD
Hypertension, n (%)	117 (49.2%)	107 (45.0%)	0.386	0.084
Diabetes mellitus, n (%)	65 (27.3%)	55 (23.1%)	0.314	0.097
Pregnancy, n (%)	32 (13.4%)	32 (13.4%)	1	0.000
Heart failure or MI, n (%)	18 (7.6%)	29 (12.2%)	0.118	0.155
COPD, n (%)	15 (6.3%)	15 (6.3%)	1	0.000
Fully vaccinated, n (%)	68 (28.6%)	58 (24.4%)	0.348	0.095
APACHE II score (ICU day 0)	19.0 [15.0–24.0]	19.0 [16.0–23.0]	0.673	0.032
Characteristics at index day (matching day)				
Respiratory support				
IMV, n (%)	233 (97.9%)	233 (97.9%)	1	0.000
NIV, n (%)	5 (2.1%)	5 (2.1%)	1	0.000
ECMO, n (%)	0 (0.0%)	0 (0.0%)	1	0.000
Respiratory parameters				
PEEP (cmH2O), median [IQR]	8.0 [8.0–10.0]	9.0 [7.0–12.0]	0.295	0.101
FiO2 (%), median [IQR]	65.0 [50.0–82.5]	60.0 [49.2–90.0]	0.962	0.005
PaO2/FiO2 ratio, median [IQR]	133.4 [97.1–192.9]	133.2 [92.8–183.6]	0.643	0.030
Organ dysfunction and treatment				
SOFA score, median [IQR]	5.0 [3.0–7.0]	4.0 [3.0–7.0]	0.826	0.028
Vasopressor use, n (%)	65 (27.3%)	65 (27.3%)	1	0.000
Corticosteroids, n (%)	222 (93.3%)	220 (92.4%)	0.855	0.033

Characteristic	Early oXiris group (n = 238)	Control group (n = 238)	P-value	SMD
Remdesivir, n (%)	134 (56.3%)	129 (54.2%)	0.704	0.042
NMBA use, n (%)	190 (79.8%)	191 (80.3%)	1	0.011
Inflammatory markers (index day)				
CRP (mg/L)	91.8 [48.6–164.9] (n=224)	86.4 [39.4–153.0] (n=216)	0.670	0.072
IL-6 (pg/mL)	264.1 [107.7–1136.5] (n=75)	131.7 [38.3–894.4] (n=80)	0.112	0.176
Ferritin (ng/mL)	1720 [889–2000] (n=122)	1186 [475–2000] (n=112)	0.220	0.287
D-dimer (ng/mL)	1619 [1024–5080] (n=238)	2308 [1177–7098] (n=234)	0.014	0.058

Panel B. Clinical outcomes

Outcome	oXiris (matched)	Control (matched)	P-value (matched)	SMD (matched)
Sample size	N = 238	N = 238		
Mortality Outcomes				
14-day mortality, n (%)	59 (24.8%)	54 (22.7%)	0.657	0.049
28-day mortality, n (%)	81 (34.0%)	80 (33.6%)	1	0.009
In-hospital mortality, n (%)	102 (42.9%)	93 (39.1%)	0.448	0.077
Secondary Outcomes				
ICU length of stay (days)	16.0 [8.0–28.0]	13.5 [8.0–22.0]	0.027	0.259
Ventilator-free days (day 28)	2.0 [1.0–8.8]	2.0 [1.0–8.8]	0.742	0.051

Data are presented as mean ± SD, median [IQR], or n (%), as appropriate. P-values for binary outcomes were calculated using conditional logistic regression, and p-values for continuous outcomes were calculated using paired non-parametric tests, as appropriate. SMD, standardised mean difference; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; ECMO, extracorporeal membrane oxygenation; NMBA, neuromuscular blocking agent; MI, myocardial infarction; CRP, C-reactive protein; IL-6, interleukin-6.

Annex 4: baseline characteristics and clinical outcomes in the wider-calliper matched cohort (0.25 SD of the logit propensity score)

Panel A. Baseline and index-day characteristics

Characteristic	Early oXiris group (n = 248)	Control group (n = 248)	P-value	SMD
Demographics and comorbidities				
Age (years), mean ± SD	58.3 ± 19.8	58.2 ± 21.1	0.969	0.003
Male, n (%)	131 (52.8%)	133 (53.6%)	0.918	0.016
Any comorbidity, n (%)	191 (77.0%)	186 (75.0%)	0.661	0.047
Hypertension, n (%)	117 (47.2%)	108 (43.5%)	0.435	0.073
Diabetes mellitus, n (%)	65 (26.2%)	58 (23.4%)	0.515	0.065
Pregnancy, n (%)	39 (15.7%)	39 (15.7%)	1	0.000
Heart failure or MI, n (%)	18 (7.3%)	25 (10.1%)	0.324	0.100
COPD, n (%)	14 (5.6%)	16 (6.5%)	0.845	0.034
Fully vaccinated, n (%)	70 (28.2%)	55 (22.2%)	0.151	0.140
APACHE II score (ICU day 0)	19.0 [15.0–24.0]	19.0 [15.0–23.0]	0.233	0.079
Characteristics at index day (matching day)				
Respiratory support				
IMV, n (%)	241 (97.2%)	241 (97.2%)	1	0.000
NIV, n (%)	7 (2.8%)	7 (2.8%)	1	0.000

Characteristic	Early oXiris group (n = 248)	Control group (n = 248)	P-value	SMD
ECMO, n (%)	0 (0.0%)	0 (0.0%)	1	0.000
Respiratory parameters				
PEEP (cmH2O), median [IQR]	8.0 [8.0–10.0]	10.0 [8.0–12.0]	0.188	0.128
FiO2 (%), median [IQR]	65.0 [50.0–81.5]	60.5 [50.0–90.0]	0.728	0.024
PaO2/FiO2 ratio, median [IQR]	131.4 [99.7–193.9]	134.8 [98.8–182.7]	0.646	0.039
Organ dysfunction and treatment				
SOFA score, median [IQR]	5.0 [3.0–7.0]	4.0 [3.0–7.0]	0.690	0.018
Vasopressor use, n (%)	69 (27.8%)	69 (27.8%)	1	0.000
Corticosteroids, n (%)	233 (94.0%)	234 (94.4%)	1	0.017
Remdesivir, n (%)	138 (55.6%)	129 (52.0%)	0.448	0.073
NMBA use, n (%)	198 (79.8%)	198 (79.8%)	1	0.000
Inflammatory markers (index day)				
CRP (mg/L)	91.2 [49.5–156.9] (n=234)	82.5 [40.0–141.8] (n=227)	0.382	0.090
IL-6 (pg/mL)	218.6 [54.7–983.2] (n=77)	100.7 [28.5–736.8] (n=82)	0.449	0.184
Ferritin (ng/mL)	1692 [814–2000] (n=130)	1200 [459–2000] (n=116)	0.318	0.238
D-dimer (ng/mL)	1646 [1018–5119] (n=248)	2237 [1112–6338] (n=243)	0.059	0.029

Panel B. Clinical outcomes

Outcome	oXiris (matched)	Control (matched)	P-value (matched)	SMD (matched)
Sample size	N = 248	N = 248		

Outcome	oXiris (matched)	Control (matched)	P-value (matched)	SMD (matched)
Mortality Outcomes				
14-day mortality, n (%)	58 (23.4%)	55 (22.2%)	0.824	0.029
28-day mortality, n (%)	80 (32.3%)	75 (30.2%)	0.685	0.044
In-hospital mortality, n (%)	101 (40.7%)	92 (37.1%)	0.456	0.074
Secondary Outcomes				
ICU length of stay (days)	17.0 [8.0–28.0]	13.0 [8.0–22.0]	0.018	0.197
Ventilator-free days (day 28)	2.5 [1.0–9.0]	3.0 [1.0–9.0]	0.963	0.004

Data are presented as mean ± SD, median [IQR], or n (%), as appropriate. P-values for binary outcomes were calculated using conditional logistic regression, and p-values for continuous outcomes were calculated using paired non-parametric tests, as appropriate. SMD, standardized mean difference; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; ECMO, extracorporeal membrane oxygenation; NMBA, neuromuscular blocking agent; MI, myocardial infarction; CRP, C-reactive protein; IL-6, interleukin-6.

Annex 5: baseline characteristics and clinical outcomes in the sensitivity analysis with additional exact matching on CRP and IL-6 quartiles

Panel A. Baseline and index-day characteristics

Characteristic	Early oXiris group (n = 38)	Control group (n = 38)	P-value	SMD
Demographics and comorbidities				
Age (years), mean ± SD	60.2 ± 20.9	60.7 ± 22.9	0.890	0.022
Male, n (%)	19 (50.0%)	20 (52.6%)	1	0.053
Any comorbidity, n (%)	33 (86.8%)	30 (78.9%)	0.450	0.211
Hypertension, n (%)	20 (52.6%)	17 (44.7%)	0.505	0.158
Diabetes mellitus, n (%)	12 (31.6%)	12 (31.6%)	1	0.000

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Characteristic	Early oXiris group (n = 38)	Control group (n = 38)	P-value	SMD
Pregnancy, n (%)	8 (21.1%)	8 (21.1%)	1	0.000
Heart failure or MI, n (%)	2 (5.3%)	6 (15.8%)	0.221	0.348
COPD, n (%)	5 (13.2%)	1 (2.6%)	0.221	0.398
Fully vaccinated, n (%)	9 (23.7%)	11 (28.9%)	0.803	0.120
APACHE II score (ICU day 0)	21.5 [17.2–23.8]	20.0 [17.2–25.5]	0.952	0.037
Characteristics at index day (matching day)				
Respiratory support				
IMV, n (%)	38 (100.0%)	38 (100.0%)	1	0.000
NIV, n (%)	0 (0.0%)	0 (0.0%)	1	0.000
ECMO, n (%)	0 (0.0%)	0 (0.0%)	1	0.000
Respiratory parameters				
PEEP (cmH2O), median [IQR]	8.0 [8.0–10.0]	10.0 [6.5–10.0]	1	0.010
FiO2 (%), median [IQR]	65.5 [60.0–80.0]	60.0 [51.2–80.0]	0.626	0.169
PaO2/FiO2 ratio, median [IQR]	135.9 [105.2–197.5]	156.8 [120.0–192.2]	0.919	0.019
Organ dysfunction and treatment				
SOFA score, median [IQR]	4.0 [3.0–6.8]	5.0 [4.0–7.0]	0.151	0.227
Vasopressor use, n (%)	9 (23.7%)	9 (23.7%)	1	0.000
Corticosteroids, n (%)	35 (92.1%)	35 (92.1%)	1	0.000
Remdesivir, n (%)	29 (76.3%)	26 (68.4%)	0.579	0.177
NMBA use, n (%)	31 (81.6%)	29 (76.3%)	0.617	0.129

Characteristic	Early oXiris group (n = 38)	Control group (n = 38)	P-value	SMD
Inflammatory markers (index day)				
CRP (mg/L)	123.7 [77.1–210.4] (n=38)	99.7 [68.1–173.5] (n=38)	0.622	0.054
IL-6 (pg/mL)	138.3 [42.3–476.1] (n=38)	146.9 [41.9–667.7] (n=38)	0.442	0.015
Ferritin (ng/mL)	1194 [790–2000] (n=28)	1624 [358–2000] (n=18)	0.363	0.013
D-dimer (ng/mL)	1894 [1030–4270] (n=38)	3319 [1647–13122] (n=38)	0.514	0.008

Panel B. Clinical outcomes

Outcome	oXiris (matched)	Control (matched)	P-value (matched)	SMD (matched)
Sample size	N = 38	N = 38		
Mortality Outcomes				
14-day mortality, n (%)	10 (26.3%)	9 (23.7%)	1	0.061
28-day mortality, n (%)	13 (34.2%)	11 (28.9%)	0.752	0.113
In-hospital mortality, n (%)	15 (39.5%)	11 (28.9%)	0.386	0.223
Secondary Outcomes				
ICU length of stay (days)	13.0 [8.0–21.0]	10.0 [5.2–15.0]	0.032	0.404
Ventilator-free days (day 28)	1.0 [1.0–6.0]	3.0 [1.0–6.8]	0.230	0.126

Data are presented as mean ± SD, median [IQR], or n (%), as appropriate. Matching was repeated with additional exact matching on CRP and IL-6 quartiles. P-values for binary outcomes were calculated using conditional logistic regression, and p-values for continuous outcomes were calculated using paired non-parametric tests, as appropriate. SMD, standardised mean difference; CRP, C-reactive protein; IL-6, interleukin-6; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; ECMO, extracorporeal membrane oxygenation; NMBA, neuromuscular blocking agent; MI, myocardial infarction. Owing to the substantially reduced matched sample size, these results should be interpreted cautiously.

Annex 6: day-3 landmark complete-case IPTW analysis (ATT): cohort definition, covariate balance, weighted outcomes, and effect estimates

Panel A. Cohort definition and weight distribution

Metric	Value
N in input D3 cohort	1007
N complete-case for PS model	769
N excluded for missing PS covariates	238
Treated (A=1) in PS cohort	264
Control (A=0) in PS cohort	505
Raw ATT weight min	0.012
Raw ATT weight p1	0.027
Raw ATT weight median	0.724
Raw ATT weight p99	2.297
Raw ATT weight max	3.546
Trimmed ATT weight min	0.027
Trimmed ATT weight max	2.297

Panel B. Covariate balance before and after weighting

Variable	Type	Unadjusted SMD	Weighted SMD	Balance after weighting
Age	Continuous	-0.319	0.067	Balanced, <0.1
Male sex	Binary	-0.117	0.027	Balanced, <0.1
APACHE II score (ICU day 0)	Continuous	-0.070	0.013	Balanced, <0.1
Chronic kidney disease	Binary	0.023	-0.000	Balanced, <0.1
Diabetes mellitus	Binary	0.026	0.011	Balanced, <0.1
Hypertension	Binary	-0.042	0.008	Balanced, <0.1

Variable	Type	Unadjusted SMD	Weighted SMD	Balance after weighting
Pregnancy	Binary	0.086	-0.028	Balanced, <0.1
SOFA score (ICU day 0)	Continuous	0.341	-0.003	Balanced, <0.1
PaO_2/FiO_2 ratio (ICU day 0)	Continuous	-0.436	0.047	Balanced, <0.1
FiO_2 (ICU day 0)	Continuous	0.155	-0.061	Balanced, <0.1
PEEP (ICU day 0)	Continuous	0.344	-0.068	Balanced, <0.1
ECMO at ICU day 0	Binary	-0.042	-0.000	Balanced, <0.1
Vasopressor use (ICU day 0)	Binary	0.053	0.008	Balanced, <0.1
Corticosteroid use (ICU day 0)	Binary	0.086	0.003	Balanced, <0.1
NMBA use (ICU day 0)	Binary	0.161	-0.006	Balanced, <0.1
Remdesivir use (ICU day 0)	Binary	-0.113	0.014	Balanced, <0.1

Panel C. Weighted outcomes and effect estimates

Outcome	Early oXiris (weighted)	Control (weighted)	Effect estimate (95% CI)	p-value
14-day mortality	19.7%	17.3%	Weighted OR 1.169 (0.749–1.824)	0.492
28-day mortality	29.5%	26.0%	Weighted OR 1.194 (0.814–1.751)	0.364
In-hospital mortality	39.4%	31.8%	Weighted OR 1.391 (0.971–1.993)	0.073
ICU length of stay	22.42	19.54	Weighted mean difference 2.876 (0.236–5.515)	0.033
Ventilator-free days on day 28	7.24	6.61	Weighted mean difference 0.632 (-0.898–2.162)	0.418

Abbreviations: IPTW, inverse probability of treatment weighting; ATT, average treatment effect in the treated; PS, propensity score; SMD, standardised mean difference; OR, odds ratio; CI, confidence interval. The IPTW analysis was performed in a day-3 landmark

complete-case cohort. Weighted event proportions are shown for binary outcomes. Effect estimates were derived from weighted regression models. Adjusted balance was considered acceptable when the absolute standardised mean difference was < 0.1.