# Perfusate cytokines concentrations during liver grafts ex-situ normothermic perfusion

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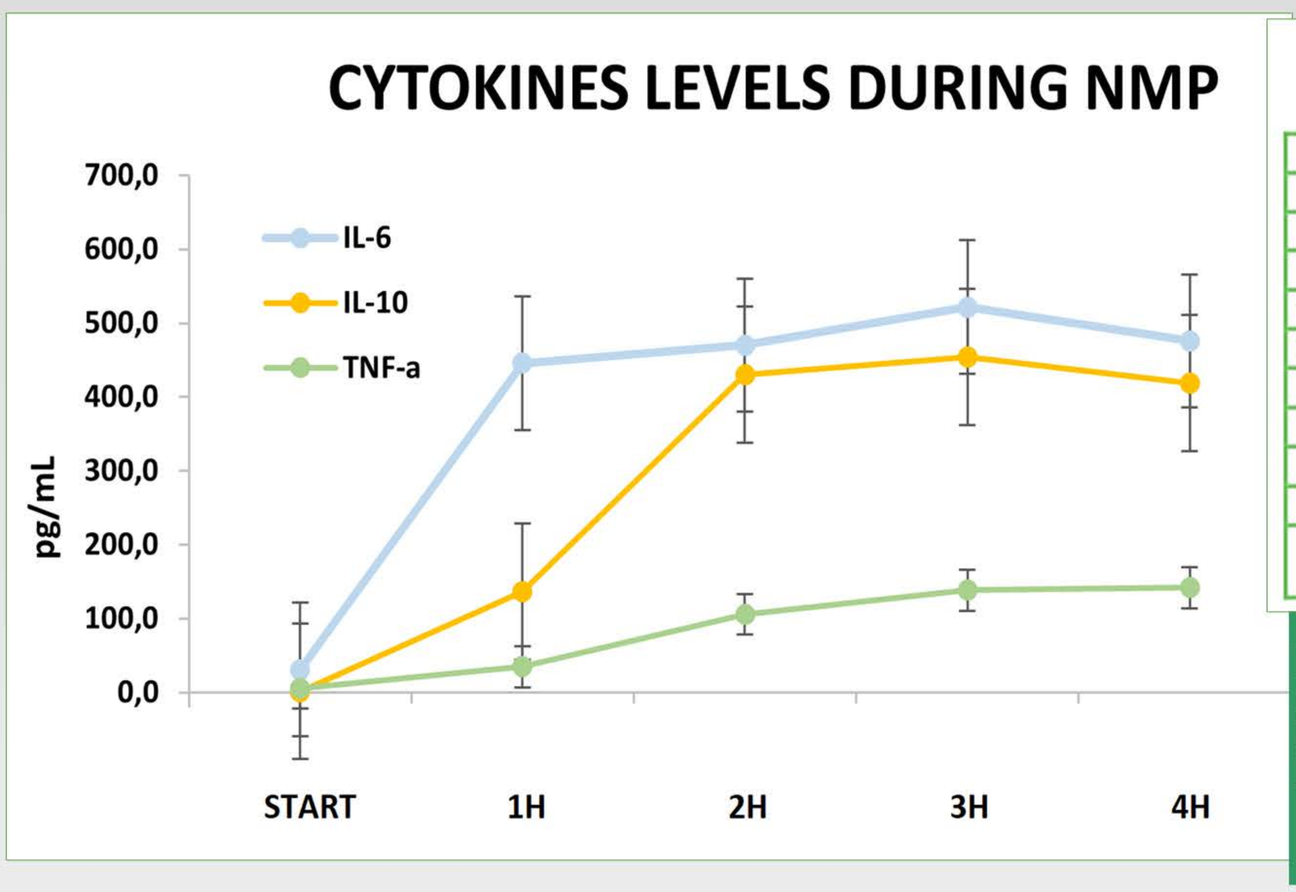
## Background

The potentialities of ex-situ normothermic machine perfusion (NMP) as a preservation method before liver transplantation are under investigation. The perfusion at normothermic conditions exposes the liver grafts to ischemia reperfusion injury, induces oxidative stress, and the release of several inflammatory cytokines that may exacerbate the damage.

## Methods

In the period from April 2016 to May 2022, we collected the perfusate of liver grafts preserved under normothermic conditions at commencing and hourly during ex-situ perfusion. All grafts were considered eligible for liver transplant and were eventually transplanted. pH, vascular flows, lactate, transaminases, glucose and cytokines (IL-6, IL-10, and TNF-alpha) perfusate concentrations, absolute value and release ratio were analyzed and correlated to clinical endpoints (graft and patients' survival, post-reperfusion syndrome, post-liver transplant renal failure, transaminases peak, early allograft dysfunction, post-operative vasopressors requirement and hospitalization length).

## Results




| | IL-6 RR | | IL-10 RR | | TNF-α RR | |
|---|---|---|---|---|---|---|
| | Median (IQR) | P | Median (IQR) | P | Median (IQR) | P |
| **Donor** | | | | | | |
| Gender (M) | 5,4 (0,1- 28) | 0,12 | 180 (32-646) | 0,85 | 15 (3-103) | 0,29 |
| Older (>80 y) | 0,486 (0,2-15) | 0,012 | 0,185 (0,1-34) | 0,37 | 0,2 (0,1-20) | 0,33 |
| DCD | 1,5 (0,1-2,7) | 0,08 | 64 (10-217) | 0,041 | 17 (3-130) | 0,59 |
| Vasopressors | 6 (0,8-1,9) | 0,17 | 359 (22-609) | 0,84 | 7 (3-24) | <0,001 |
| Hypertension | 6 (0,8-29) | 0,17 | 110 (40-515) | 0,45 | 10 (3-62) | 0,15 |
| **Recipient** | | | | | | |
| PRS | 7 (2-29) | 0,8 | 217 (56-437) | 0,99 | 13 (5-299) | 0,96 |
| AKI | 16 (6-28) | 0,7 | 515 (144-682) | 0,02 | 37 (3-310) | 0,78 |
| EAD | 7 (4-30) | 0,99 | 432 (114-680) | 0,56 | 31 (8-56) | 0,81 |
| Retransplant | 1,5 (0,8-29) | 0,44 | 572 (323-3483) | 0,24 | 21 (16-180) | 0,65 |

**ABBREVIATIONS: RR – release ratio; DCD – Donation after Circulatory Death; DBD – Donation after Brain Death; PRS Post Reperfusion Syndrome; AKI acute kidney injury** (AKI is defined as any of the following: - Increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hours; or - Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or -Urine volume <0.5 ml/kg/h for 6 hours)**; EAD early allograft dysfunction.**

**RR = (cytokine concentration at MP 2 H – cytokine concentration MP start)/ cytokine concentration MP start**

Twenty-six liver grafts (16 DBD, 10 DCD) were evaluated. Preliminarily, a cytokine profile during NMP was built and the potential influence of confounding factors (donor type, age, gender and comorbidities, ischemic times, pre-procurement lab data) was assessed. The median donor age was 77 years (IQR: 27-87), the median duration of ex-situ perfusion was 250 minutes (IQR 200-302). IL-6, IL-10, and TNF-alpha showed a peak at the third hour of perfusion and decreased thereafter. IL-6 release ratio was higher in older donor (p=0.012), IL-10 release ratio was higher in DCD donor type (p=0.041), while the TNF-alpha release ratio increased when donors required high doses of vasopressors (p<0.001). At univariate analysis, a higher IL-10 release ratio was associated to a more severe risk of developing acute kidney injury (AKI) after liver transplantation.

## Conclusions

Cytokines profiles stabilize 3-hours after commencing normothermic machine perfusion. A higher IL-10 release ratio correlates to the development of kidney injury after liver transplantation. In viable liver grafts, cytokines (IL-6, IL-10, and TNF-alpha) release ratio and absolute concentrations do not correlate to graft or patient survival.

**References**

Ghinolfi D, Melandro F, Patrono D, Lai Q, Carlis RD, Camagni S, A new ex-situ machine perfusion device. A preliminary evaluation using a model of donors after circulatory death pig livers. Artif Organs. 2022;00:1–7.