Association between mRNA expression of CD74 and IL10 and risk of ICU-acquired infections. A multicenter cohort study

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PIONEERING DIAGNOSTICS

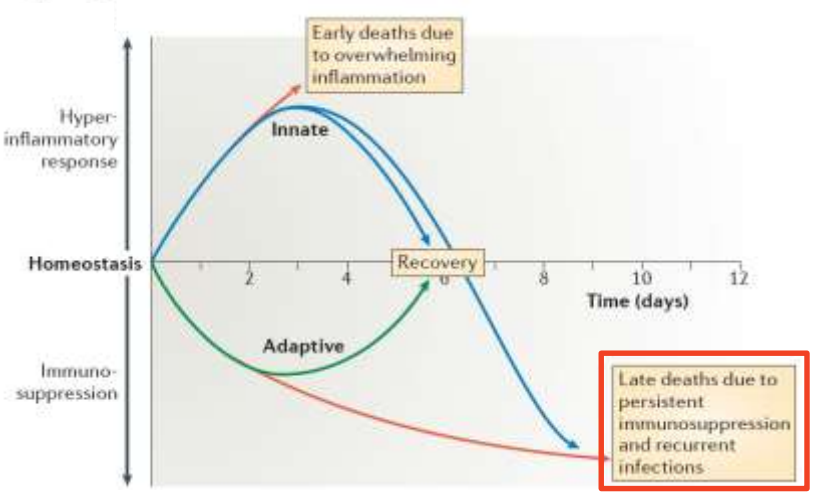
Conflicts of interest

Employee of bioMerieux.

This project is part of Advanced Diagnostics for New Therapeutic Approaches, a program dedicated to personalized medicine, coordinated by Institut Mérieux and supported by the French public agency BPI.

ICU-acquired infections (IAI)

Injury-induced immunosuppression concept



Hotchkiss et al., Nat Rev Immunol, 2013

IAI prevalence:

Up to **30% of ICU patients** with at least one IAI episode in high income countries

WHO, Report on the Burden of Endemic Health Care-Associated Infection Worldwide, 2011

Impact of IAI

- ICU and hospital lengths of stay
- healthcare costs

Vasudevan et al., Antimicrob Resist Infect Control, 2015
Rahmqvist et al., Am J Infect Control, 2016

Identification of patients at risk of IAI

⇨ Specific **preventive** procedures

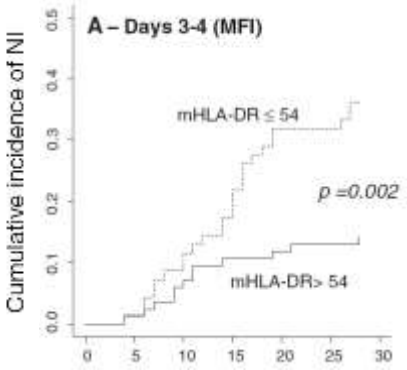
⇨ **Patients stratification** in clinical trials evaluating immuno-adjuvant therapies

Biomarkers for IAI risk assessment

Biomarkers and IAI occurrence

Monocyte HLA-DR

- Low expression in patients who will develop IAI

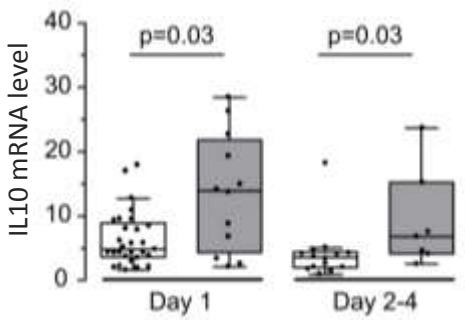


Septic shock patients

Landelle et al., Intensive Care Med, 2010

IL-10

- High expression in patients who will develop IAI



Pediatric ICU patients

IAI

No IAI

* p < 0.01

Peronnet et al., PlosOne, 2016

CD74: MHC class II-associated invariant chain

Study objective

To confirm the association between **CD74** or **IL10 mRNA expression** and **IAI occurrence**

Patients flow chart and clinical characteristics

Clinical parameters	Total n=725
Age	65 [54-76]
SAPS II	56 [42-69]
SOFA score	9 [6-12]
Trauma	67 (9.2%)
Shock	467 (64%)
Infection at admission	506 (70%)
Septic shock	255 (35%)
ICU length of stay (Days)	7 [4-14]
Survivors at day 28	516 (71%)

Heterogeneous cohort
Patients with or without **infection**
with or without **shock**

Patients enrollment
6 ICU in 3 hospitals
SIRS due or not to an infection

Total patients with sample on Day 1
N=725

Whole blood collection

CD74 & **IL10** mRNA expression

Patient follow-up
Day 3: N= 220
Day 3 + Day 6: N=267
Day 6: N= 57

ECDC definition
Suetens et al., J Hosp Infect, 2007

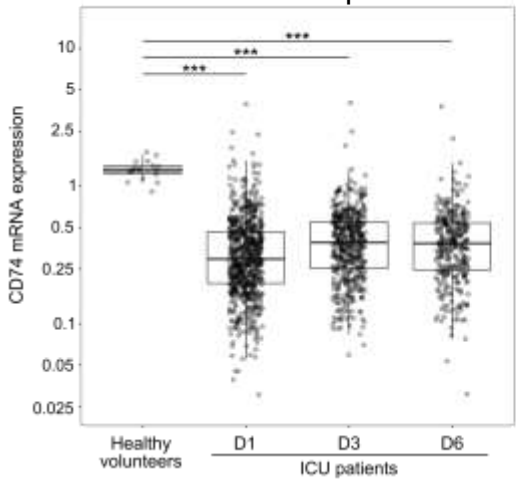
IAI
N=137 **(19%)**

Time to IAI 10 [6-18] days

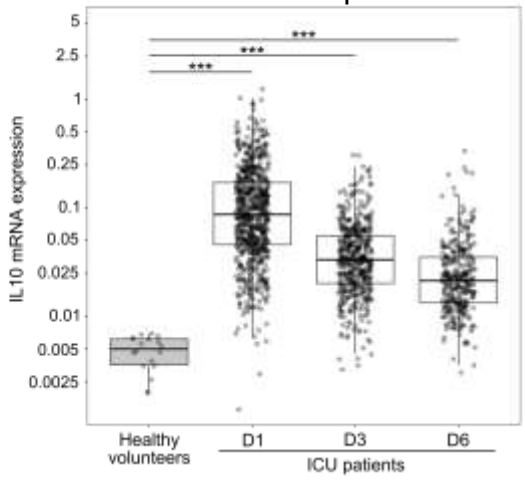
No IAI
N=588

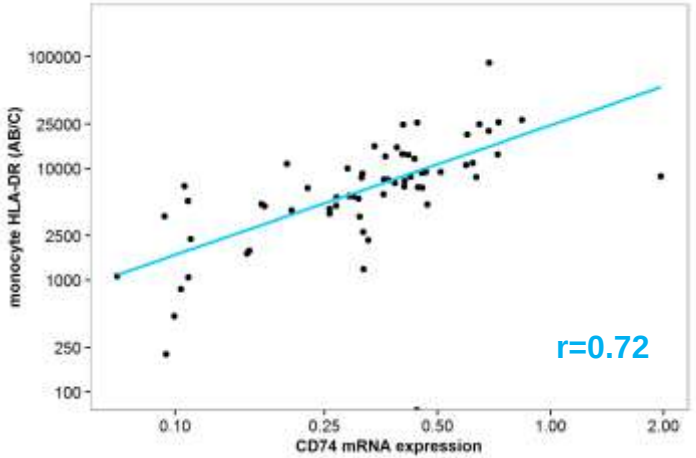
CD74 and IL10 expression in ICU patients

CD74 mRNA expression



IL10 mRNA expression





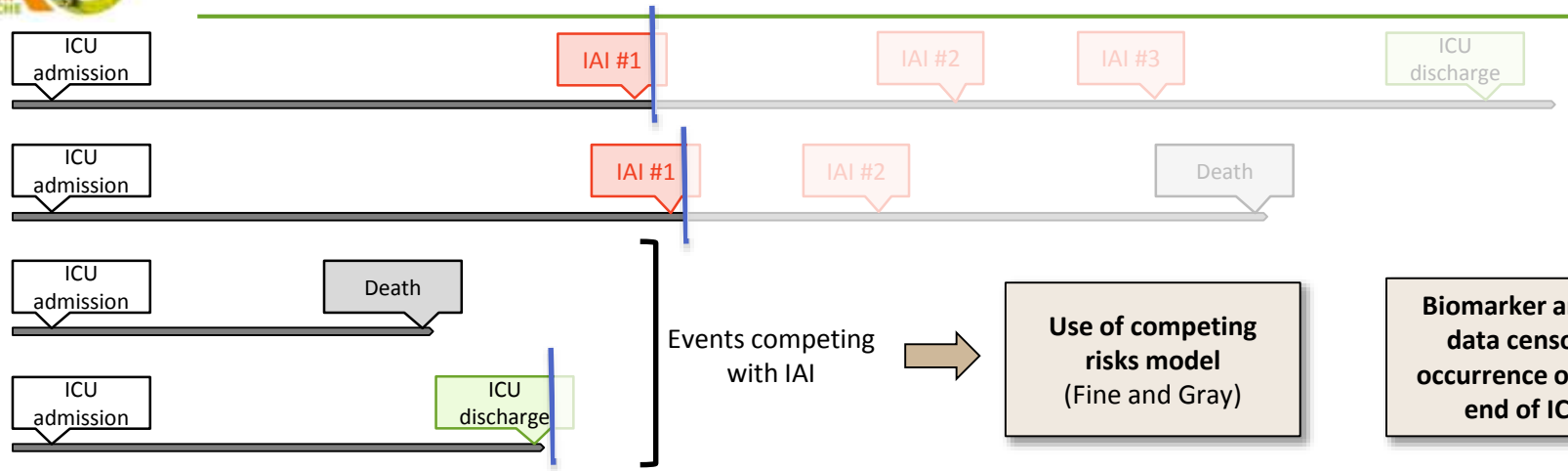
Low CD74 level in ICU patients

High IL10 level in ICU patients

Strong positive correlation between CD74 mRNA and mHLA-DR

- No correlation of CD74 or IL10 expression with severity or with cell count

Data analysis for association study



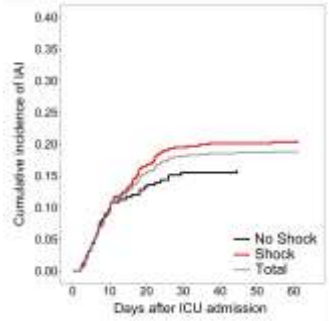
Events competing with IAI

Use of competing risks model (Fine and Gray)

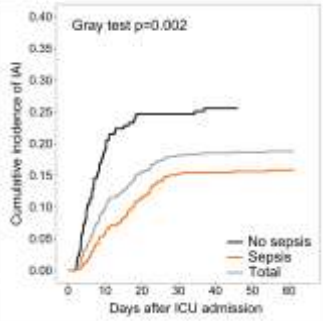
Biomarker and clinical data censor at the occurrence of 1st IAI or end of ICU stay

IAI cumulative incidence

Shock status



Sepsis status



Confounding factors for IAI occurrence

Shock and sepsis status at admission in **multivariate** models

CD74 and IL10 are associated with IAI occurrence

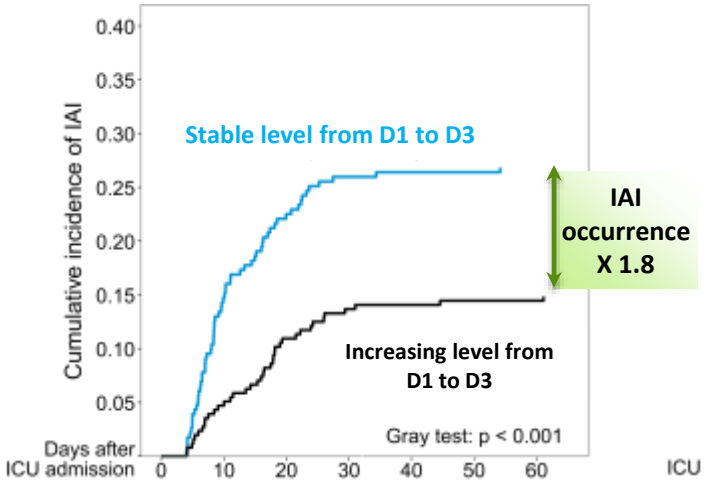
Association with IAI occurrence (Fine and Gray models)

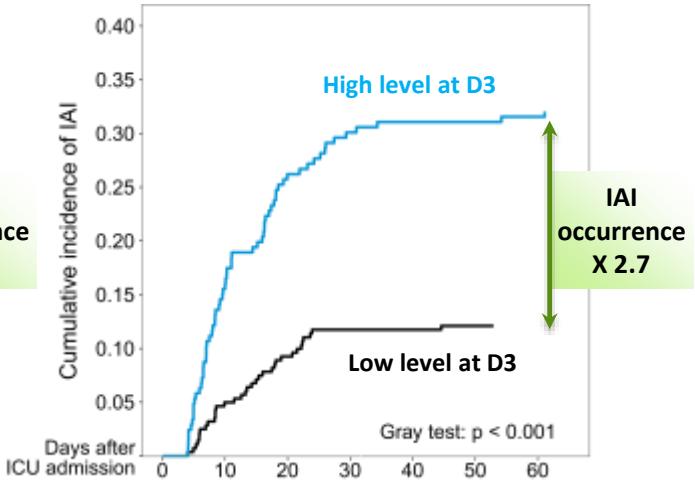
CD74		
Variable	**sdHR (95% CI)**	**p-value**
CD74 D3/D1	0.67 (0.46-0.97)	**0.033**
Shock	1.79 (1.14-2.8)	**0.012**
Sepsis	0.53 (0.35-0.81)	**0.003**

IL10		
Variable	**sdHR (95% CI)**	**p-value**
IL10 D3 *	2.21 (1.63-3.00)	**<0.001**
Shock	1.68 (1.07-2.64)	**0.025**
Sepsis	0.56 (0.37-0.85)	**0.006**

* sdHR expressed for an increment of 0.1 unit

Patients stratification according to **CD74** or **IL10** expression





Conclusions and perspectives

- **Confirmation of the association between CD74 or IL10 mRNA level with IAI occurrence**, independently of sepsis and shock status at admission, in a large multicenter study
- **Different IAI incidence in patients groups stratified on CD74 D3/D1 ratio or IL10 D3 mRNA expression level**

Manuscript accepted in Intensive Care Medicine

Stratification biomarkers in multicenter clinical trials evaluating immuno-adjuvant therapies

Perspectives

Patient stratification

CD74 or **IL10** assay

Low risk
(High CD74 or low IL10)

High risk
(Low CD74 or high IL10)

Placebo

Treatment

Immunoadjuvant therapy evaluation
(GM-CSF, IL-7, anti-PD-L1, IFN-γ,…)

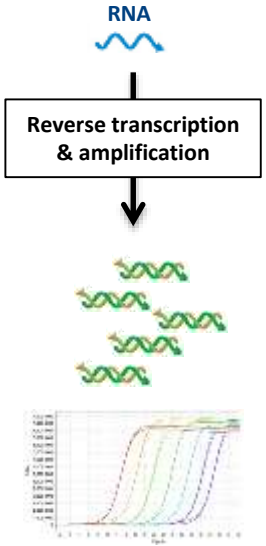
Contact for collaboration: estelle.peronnet@biomerieux.com

Perspectives

Available now for clinical validation

Standardized molecular biology assays

- RUO RT-qPCR assays
- Compatible with several PCR platforms



Tomorrow…

… patients stratification in **clinical routine**, near-patient molecular biology-based testing

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Thanks to…

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