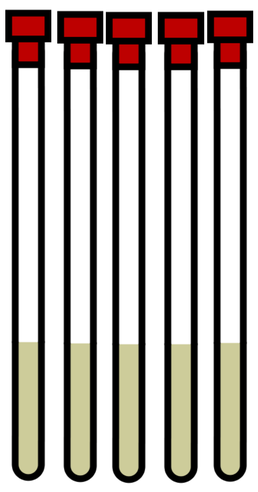
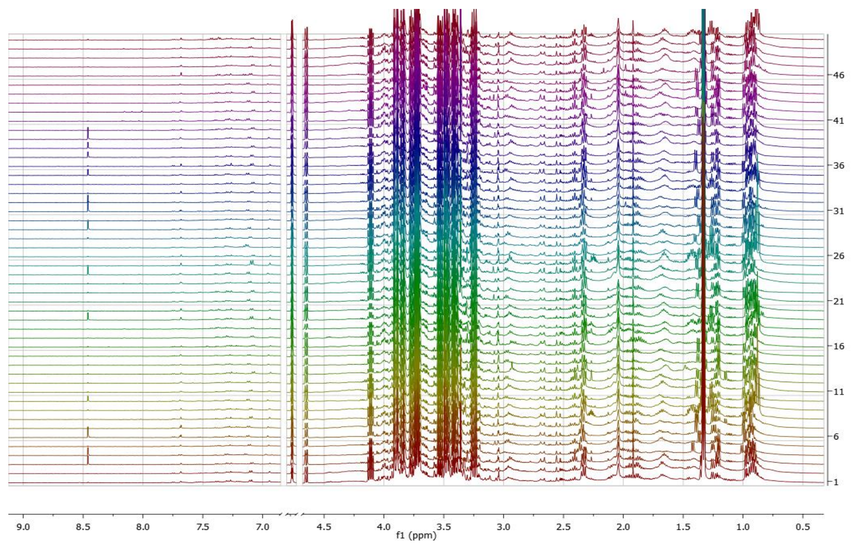
Application of metabolomics in drug-resistant epilepsy research

Federica Murgia[1], Simone Poddighe[1], Francesco Del Carratore[1], Lorenzo Polizzi[2], Antonella Muroni[2], Luigi Barberini[3], Monica Pulighedду[3], Francesco Marrosu[2] , Luigi Atzori[1]

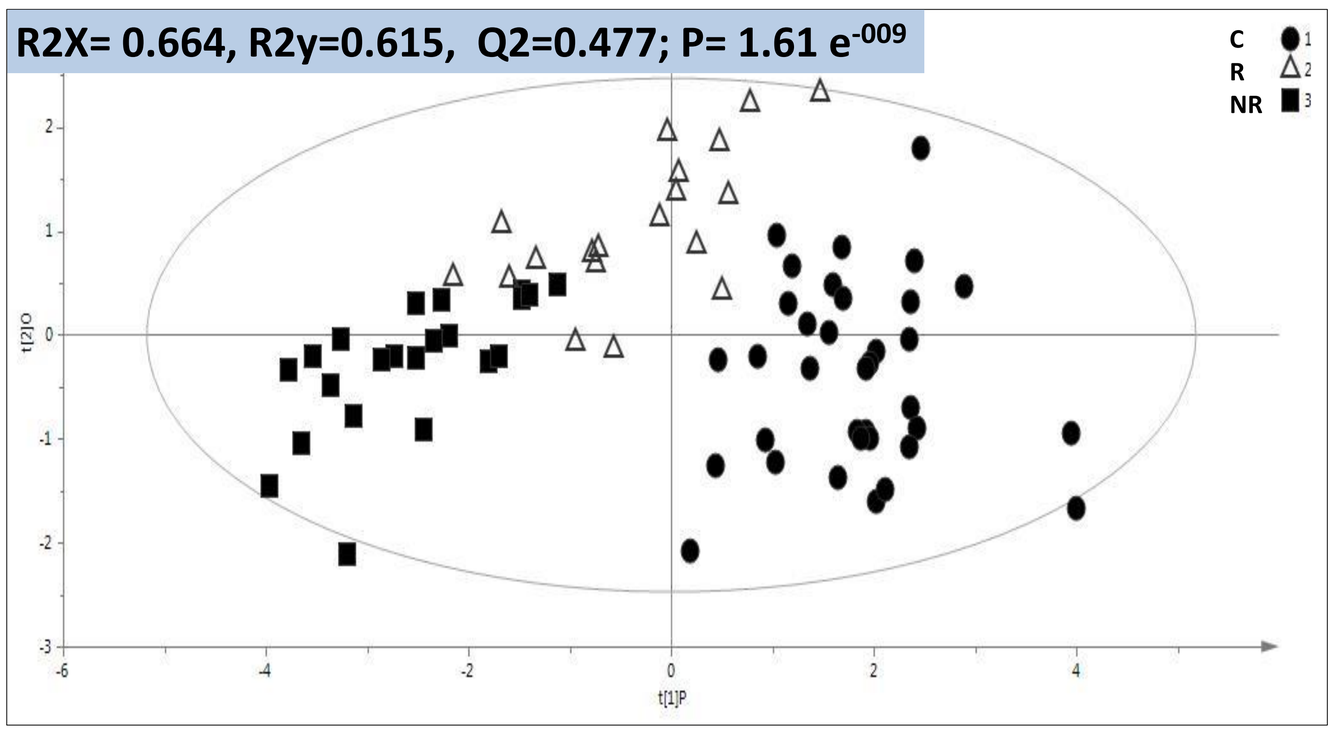
1 Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy.
2 Department of Medical Sciences,
3 Department of Public Health, Clinical and molecular medicine

Introduction: Drug resistance is a critical issue in the treatment of epilepsy. Drug resistance determines the presence of disabling seizures, which lead the affected individual to a significant neuropsychiatric and social impairment(1). One third of people with epilepsy are resistant to old and new antiepileptic drugs. For these reasons and for the economic impact of this phenomenon it is necessary an early detection strategy for patients will not be suitable for new attempts to drug therapy. Metabolomics could provide the tool for to investigate possible markers of drug resistance in a population of epileptic subjects suggesting also a possible mechanism(2).



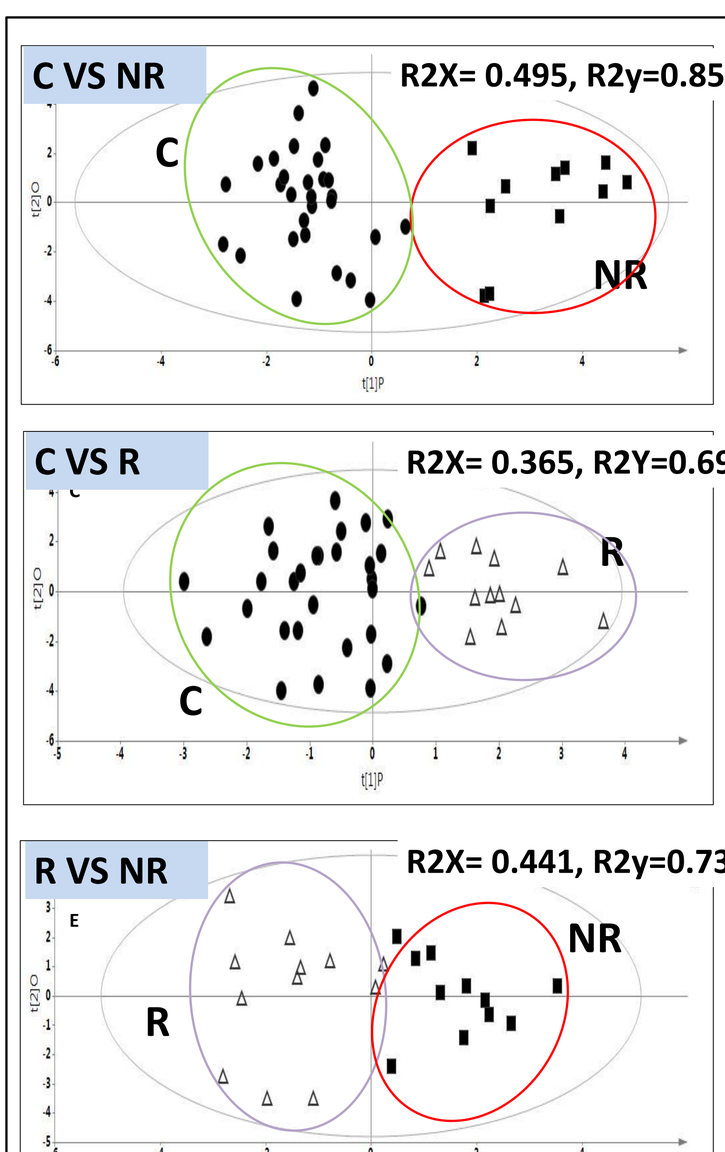


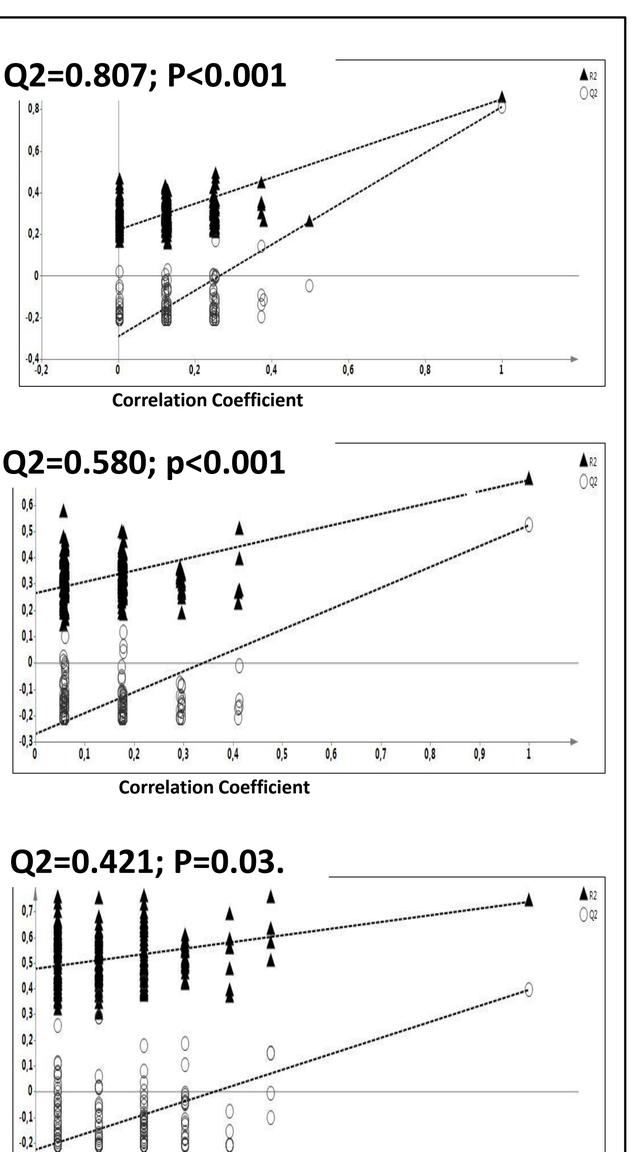
Materials and methods: Blood samples were collected from 3 groups: 1) healthy patients (n=35); 2) patients "responder" (R) to the drug therapy (n=18), and 3) patients "not responder" (NR) (n=17). The samples were analysed by using a Varian UNITY INOVA 500 spectrometer. Multivariate statistical analysis was performed by using SIMCA-P+ software. The metabolites corresponding to the discriminant variables were identified and quantified by using Chenomx software



Results: The group of the pathological patients were characterized by an increase of acetate, acetoacetate, acetone and scyllo-inositol compared to controls group, and a decrease in lactate, glucose and citrate. The metabolic fingerprint of the class of NR was significantly different from R based on increased levels of ketone bodies

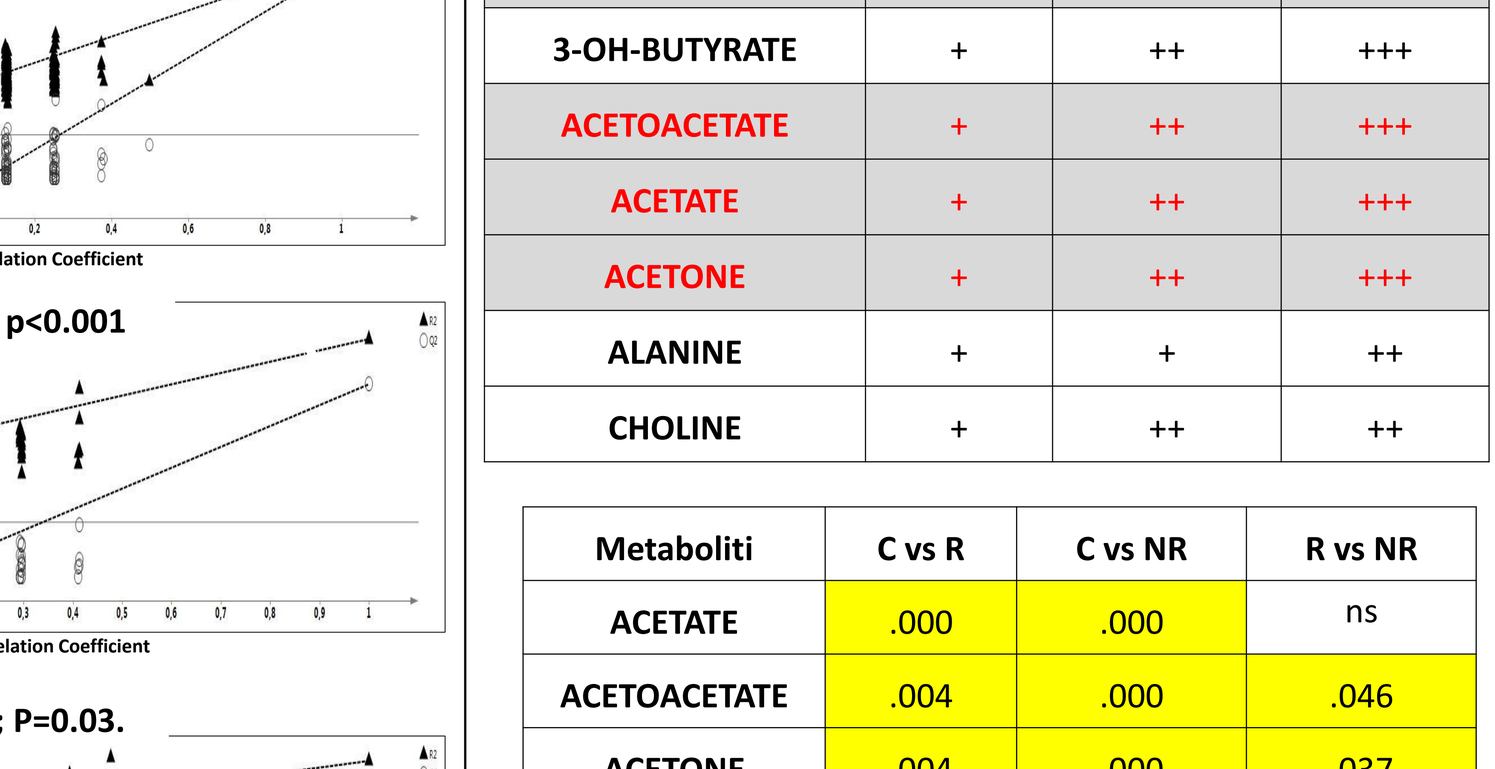
Metabolites	C	R	NR
CITRATE	+++	++	+
LACTATE	+++	++	+
GLUCOSE	+++	++	+
GLUTAMATE	++	+	++
SCYLLO-INOSITOL	+	+++	+
3-OH-BUTYRATE	+	++	+++
ACETOACETATE	+	++	+++
ACETATE	+	++	+++
ACETONE	+	++	+++
ALANINE	+	+	++
CHOLINE	+	++	++





Metaboliti	C vs R	C vs NR	R vs NR
ACETATE	.000	.000	ns
ACETOACETATE	.004	.000	.046
ACETONE	.004	.000	.037
CITRATE	ns	.012	ns
GLUCOSE	ns	.039	ns
LACTATE	ns	.000	.001
SCYLLO INOS.	.011	ns	ns

Conclusions: Metabolomics represents an important tool for biomarker discovery in drug-resistant epilepsy and for the study of the pathophysiology of this disease.



1) Pati S. and Alexopoulos AV, Pharmacoresistant epilepsy: From pathogenesis to current and emerging terapies, Cleve Clin J Med 2010; 77:7457-467.
2) Sinclair AJ, Viant MR, Ball AK, et al. NMR-based metabolomic analysis of cerebrospinal fluid and serum in neurological diseases-a diagnostic tool? NMR Biomed. 2010;23(2):123-32.