Metabolic profiling reveals interleukin-17A monoclonal antibody treatment ameliorate lipids metabolism with the potentiality to reduce cardiovascular risk in psoriasis patients

Cao Han
Fudan University
Su Shengmin
Fudan University
Yang Qi
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Le Yunchen
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Chen Lihong
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Hu Mengyan
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Guo Xiaoyu
Fudan University
Zheng Jie
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Li Xia
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Yunqiu Yu (yqyu@shmu.edu.cn)
Fudan University https://orcid.org/0000-0002-5629-8753

Research

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Abstract

Background: Psoriasis is a common chronic inflammatory skin disease associated with the overproduction of interleukin-17A. It has been reported that psoriasis patients had an increased risk of cardiovascular diseases. Ixekizumab is a humanized IgG4-κ monoclonal antibody which has shown efficacy in psoriasis patients. Although the pathogenesis in psoriasis and cardiovascular diseases have a remarkable resemblance, the underlying mechanism of two diseases and the possibility of IL-17A monoclonal antibody in the amelioration of cardiovascular comorbidities remains unclear.

Methods: Serum samples of two study cohorts including 117 individuals were analyzed using high throughput UHPLC-MS platform. Non-target metabolic profiling analysis was firstly conducted between healthy people, psoriasis patients and Ixekizumab treated patients in study cohort 1. The second study cohort was additionally recruited to validate the correlation of the identified metabolites and cardiovascular diseases.

Results: A total of 43 differential metabolites including lysophospholipids, acyl-carnitines and dicarboxylic acids were accurately identified in study cohort 1, which showed impaired lipids metabolism in psoriasis patients. Results of the study cohort 2 largely conform to the previous observations in study cohort 1. Moreover, all identified LPCs levels were higher in psoriasis patients with coronary heart diseases compared with psoriasis patients. It was worth noting that most of these lipidic changes were ameliorated after receiving Ixekizumab treatment.

Conclusion: In this non-target metabolic analysis, we found the treatment of IL-17A monoclonal antibody not only can ameliorate the lesions of psoriasis, but also restore the dysregulated lipids metabolism to normal in psoriasis patients. Considering dysregulated lipids metabolism has been regarded as the critical factor in cardiovascular diseases, the recovery of lipidic metabolites in psoriasis patients indicated that IL-17A mAb might have the potential protective effect on cardiovascular comorbidities.

1. Introduction

Psoriasis is one of the most common chronic inflammatory skin diseases with metabolic and cardiovascular comorbidities[1]. Association of cardiovascular diseases (CVDs) with psoriasis was noticed since 1890s[2]. Increased risk of CVDs in psoriasis patients has been reported by a number of studies[3–5]. In addition to the abnormal immune cell responses observed in the pathogenesis of psoriasis, recent pathophysiological insight focused on the activation of IL-23/IL-17 axis, which enhances keratinocyte abnormal proliferation and induces psoriasis[6]. Although the exact role of IL-17A in CVDs is still debatable, aggregated IL-17 producing cells and enhanced IL-17A were observed in atherosclerotic lesions [7, 8]. The theory of “two plaques for one syndrome” was proposed since molecular mechanisms of these two diseases bear a remarkable resemblance of T cells mediated inflammation[9]. Although the increased risk of CVDs in psoriasis patients may partly be explained by the hypothesis that chronic skin inflammation and the concomitant proinflammatory cytokines promoted the development of CVDs, the

underlying mechanisms remain unclear[10]. Ixekizumab, a recombinant humanized IgG4-κ monoclonal antibody which selectively binds and neutralizes IL-17A, has been employed clinically in psoriasis since 2015[11]. The correlation between two diseases and its effect on cardiovascular comorbidities has aroused great concerns. It was reported that one-year IL-17 mAb therapy reduced lipid-rich necrotic core, providing evidence that the systemic treatment of psoriasis with IL-17 mAb may have potential benefit on CVDs [12].

As an important member of the 'omics field', metabolomics is capable of indicating the complex interaction between the individual genetic inheritance and constantly changing environment by measurement and identification of small-molecule metabolites[13]. However, published metabolic analyses of psoriasis or CVDs mainly focused on pathophysiologic mechanisms between patients and healthy people, respectively[14, 15]. On the hand, although several biologic agents have been successfully used in the treatment of psoriasis and have an acceptable safety and tolerability, rare study is focused on the altered lipidic profiling before and after biologic agent treatment in psoriasis patients.

Considering the remarkable resemblance of pathogenesis in psoriasis and CVDs, we using high throughput ultra-performance liquid chromatography mass spectrometry (UHPLC-MS) platform to analyze the metabolic alterations in IL-17A mAb treated psoriasis patients to provide insight into the potential convergent mechanism in psoriasis and CVDs (Fig. 1). Impaired lipids metabolism differentiated in psoriasis patients was demonstrated to be significant as well in the psoriasis patients with CVDs comorbidities in the two study cohorts. It worth pointing out that most lipidic alterations were ameliorated after 12-week Ixekizumab treatment. Considering dysregulated lipid metabolism has been regarded as the critical factor of cardiovascular events, the recovery of lipidic profiling in psoriasis patient indicated that IL-17A mAb may have potential protective effect on CVDs. Although the underlying mechanism that higher incidence of CVDs in the population with psoriasis is not fully understood, study on the lipidic changed metabolites associated with IL-17A mAb provided a foundation of future in-depth research on the pathogenesis of psoriasis.

2. Methods

2.1 Patients and ethics statement

The study cohort 1 of 28 psoriasis patients were treated with Ixekizumab which is strictly in accordance with the standard usage and dosage of the product. Serum samples were collected from psoriasis patients treated Ixekizumab at baseline and 12 weeks after treatment. Written informed consent was obtained from each patient before enrollment. The second study cohort of psoriasis patients were complicated with coronary heart diseases, defined as coronary computed tomography angiography revealing one or more atherosclerotic lesions with moderate (50–70%) or severe (> 70%) lumen stenosis. Healthy controls matching by age (within two years) and gender were collected from a physical examination center of Ruijin Hospital Shanghai Jiao Tong University, who served as the healthy control group. This study included all the healthy controls and participants in two study cohorts were recruited

from Ruijin Hospital (Table 1). For serum collection, all samples were collected in EDTA tubes, centrifuged for 5 minutes at 3000 rpm within 4 h to collect serum and immediately frozen at -80 °C until processing.

Table 1
Demographic information on the two study cohorts

	Cohort 1			**Cohort 2**			
	CON (n = 28)	PSO (n = 28)	IXE (n = 28)	CON (n = 17)	PSO (n = 17)	PC (n = 17)	CV (n = 10)
Male/Female	19/9	19/9	19/9	13/4	15/2	14/3	8/2
Age (years)	45 ± 11.6	45 ± 11.5	45 ± 11.5	62 ± 6.6	60 ± 7.1	63 ± 7.3	68 ± 14.3
BMI	24.1 ± 2.8	24.9 ± 2.8	26.1 ± 3.1	23.9 ± 2.4	24.1 ± 3.1	24.9 ± 3.9	23.3 ± 2.4
PASI	n/a	24.4 ± 8.7	0.4 ± 0.3	n/a	21.70 ± 12.2	16.87 ± 15.99	n/a
Values are reported as mean ± SD							
BMI: body mass index; PASI: psoriasis area and severity index							

2.2 Mass spectrometry

120 μL of cold methanol containing internal standards were mixed with 30 μL of serum, vortexed for 5 min and then kept at room temperature for 10 minutes to allow protein precipitation. Hexadecylamine and tridecanoic acid (Sigma-Aldrich, St. Louis, MO) were used as internal standard in positive mode and negative mode, respectively. After centrifuged at 12000 rpm for 5 min, supernatant was collected for UHPLC-MS analysis. Quality control samples (QCs) were obtained by mixing 20 μL from each serum sample.

UHPLC-MS analysis was conducted on a 1290 Infinity UHPLC systems coupled to a 6530 iFunnel ESI-Q-TOF mass spectrometry (Agilent Technologies, Germany) which employed with a degasser, binary pump and thermostated autosampler. Chromatographic separation was carried out on an ACQUITY UPLC HSS T3 column (2.1 mm x 100 mm, 1.8 μm, Waters, USA) with 0.1% formic acid in both water (A) and acetonitrile (B) as the mobile phase. Mobile phase A was kept at 99% for the first 1 min and decreased linearly to 60%, 50% and 35% in the next 4 min, 3 min and 8 min sequentially under the flow rate of 0.3 mL/min. During 8 to 16 min, mobile phase A further decreased to 24% and finally decreased to 0% and maintained for 5 min. 10 uL of each sample was injected and the column was held at a constant temperature of 35 °C. QCs were analyzed at regular intervals throughout the whole analytical run.

Real time mass calibration was carried out by monitoring two reference compounds *mz* 121.0509 and *m/z* 922.0098 in the positive mode and *m/z* 112.9856 and *m/z* 1033.9881 in negative mode. Acquisition were carried out at 32,000 resolutions in centroid mode and one spectrum per second in the 50-1050 m/z range. ESI source parameters were set as following: nitrogen as desolvation gas at 10 L/min, nebulizer pressure at 40 psi and fragmentor voltage at 175V. The capillary voltage of ESI was set at 3500V and gas temperature was set at 350 ℃.

2.3 Data analysis

Raw data was acquired by MassHunter workstation and converted to mzData by MassHunter Qualitative Analysis software (B.06.00). Further data processing was conducted on XCMS-Online (https://xcmsonline.scripps.edu) including feature detection, peak alignment and retention time correction. Intensity of each feature was corrected by the response of the internal standard in the same sample before statistical analysis.

Identification procedure of metabolites was done according to rules set out by the Chemical Analysis Working Group of the Metabolite Standards Initiative[16]. Criterion was set for feature selection as *p*-value < 0.05 from t-test analysis and variable importance in projection (VIP) > 1 from orthogonal partial least squares discrimination analysis (OPLS-DA). Identified metabolites was labelled as level 1 if confirmed with reference standards or as level 2 if MS/MS spectra matched with that from the Human Metabolome Database (www.hmdb.ca) when reference standards was not available[17]. MS/MS analysis was also conducted on the same mass spectrometry. A table of three collision energy (10 eV, 20 eV and 40 eV) in MS/MS analysis was conducted on an additional scan followed the precursor ion full scan. All the serum samples and reference standards were conducted the same MS/MS method and injection volume in order to standardize the comparison.

2.4 Chemometrics

Raw data was logarithmically transformed and tested for normality before comparison of mean between different groups. If normality was assumed, student t-test was applied, otherwise non-parametric method was used. In study cohort 1, test of mean difference between control and psoriasis groups was analysis by student t-test if the assumption of normality was met. For psoriasis group and Ixekizumab-treated group, paired t-test was applied when normality assumption was met, otherwise Wilcoxon method was used. In study cohort 2, Anova analysis was performed for the test of means among four groups and Dunnett-t for post-hoc comparison against the control group. Mean comparison of psoriasis patients with coronary heart diseases (PC) group and psoriasis patients (PSO) group was based on independent t-test if normality was met. For six individuals received Ixekizumab treatment in the PC group, paired t-test was applied when normality assumption was met, otherwise Wilcoxon method was used. All above mentioned statistical analyses were performed in SPSS v20 (IBM, USA). Linear regressions models, prediction plots and ROC curves were performed using Prism 8.0. In order to visualize the differentiation between different groups, principal components analysis (PCA), sparse partial least squares discriminant analysis (sPLS-DA) and orthogonal partial least squares discriminant analysis (OPLS-DA) were performed using Meatboanalyst 4.0 (http://www. metaboanalyst.ca/.).

3. Results

3.1 Non-target metabolomics reveals the metabolic profiling of psoriasis patients before and after Ixekizumab treatment

In the first step, metabolic profiling analysis was conducted in the study cohort 1 including healthy people (CON), psoriasis patients (PSO) and Ixekizumab treated patients (IXE). After raw data filtering and simple processing, processed data were carried out on PCA. Whether in positive ion or negative ion mode, IXE group was invariably between the CON and PSO groups, which indicated the metabolic profiling of Ixekizumab-treated psoriasis patients converted into normal status (Fig. S1a, b). To better investigate the abnormal metabolites caused different metabolic profiles, OPLS-DA was using in following PSO/CON and IXE/PSO paired-comparisons (Fig. S1c-f).

According to the constructed multivariate models, in conjunction with univariate statistical analysis, 37 differential metabolites were revealed in PSO/CON comparison (Fig. 2) and 31 differential metabolites were accurately identified in IXE/PSO comparison (Fig. S2). In total of 43 metabolites including lysophospholipids (LPLs), free fatty acids (FFAs), dicarboxylic acids (DAs) and acyl-carnitines that contributed most to the differentiation of groups was identified in the study cohort 1 (Table S1).

Receiver operating characteristic (ROC) curve analysis is generally considered to be the gold standard for the assessment of biomarkers performance. Given that area under the curve (AUC) of ROC curves was high than 0.6, these identified metabolites could be regarded as candidate biomarkers in the Ixekizumab treated psoriasis patients (Fig. S3).

3.2 IL-17A monoclonal antibody ameliorate dysregulated lipids metabolism in psoriasis patients

As visualized in the heat map, LPLs and FFAs were upregulated in psoriasis patients compared with healthy people, while DAs and acyl-carnitines were altered in the opposite way (Fig. 3a). Lysophosphatidylcholines (LPCs), lysophosphatidylinositols (LPIs) and lysophosphatidic acids (LPAs) were significantly upregulated in the psoriasis patients. It has been demonstrated that the circulating LPCs and LPAs have the potent pro-inflammatory effect and raised in the several inflammation-associated diseases including psoriasis[18, 19]. Moreover, the presence of n-6 polyunsaturated fatty acids on LPCs have the stronger ability to evoke inflammatory response[20]. In this study, LPC (22:5) and LPC (20:3) with n-6 polyunsaturated fatty acids had highest fold-change values among all the identified LPCs (Fig. 3b). In accordance with the increased levels of LPCs, as its downstream product, glycerophosphocholine (GPC) level was also explosively upregulated in psoriasis patients (Fig. 3b). As LPCs can be produced by phosphatidylcholines, decreased levels of phosphatidylcholines further proved disordered phospholipids pathway. In addition to LPCs, another LPLs, LPIs were also upregulated in psoriasis patients (Fig. 3b). Although LPIs have relatively lower concentration in human blood compared with LPCs, they have abundant biological functions including pro-inflammatory[21].

In the Land's cycle, FFAs can be produced from LPLs by phospholipase A [22]. As expected, FFAs levels were likewise higher in the serum of psoriasis patients. Compared with upregulated FFAs, DAs and acyl-

carnitines decreased in psoriasis patients (Fig. 3b). Since DAs were the intermediates in the ω-oxidation pathway and acyl-carnitines were the “vehicles” in the β-oxidation process, decreased levels of these two metabolites indicated potential dysfunction of fatty acids decomposition and in turn result in higher blood levels of FFAs. Accumulation of FFAs has been reported to constantly sensitize dendritic cells to amplify Th1/Th17 immune responses [23], which was supported by the inverse correlation between DAs levels and psoriasis area and severity index (Fig. 3c).

After Ixekizumab treatment, the most obvious metabolic changes in psoriasis patients were the decreased LPCs and GPC. Especially the aforementioned inflammation-associated LPC (20:3) and LPC (22:5) were drastically decreased in the treated patients. With the decrease of LPCs, PCs increased synchronously and returned to the normal levels together. The downstream product of LPCs, GPC showed the most decreased trend among all the differential metabolites, which could be explained by the decreased LPCs. Average levels of acyl-carnitines and FFAs were ameliorated at the same time although not statistically significant. However, DAs were upregulated to normal levels in treated patients. These results highlighted that the treatment of IL-17A mAb might not only ameliorate the lesions of psoriasis, but also restore the dysregulated lipids metabolism to normal level in psoriasis patients.

3.3 Common and specific metabolites in psoriasis patients with or without cardiovascular comorbidities

Out of the 43 identified metabolites in study cohort 1, 18 differential metabolites overlapped with previously reported potential biomarkers of CVDs[24]. To validate the correlation of the identified differential metabolites and CVDs, the second study cohort was recruited with additional groups of psoriasis patients with coronary heart diseases (PC) and coronary heart diseases patients without psoriasis (CV). Considering psoriasis patients with cardiovascular comorbidities were mainly elderly and age was the critical factor in the CVDs, additional healthy people (CON) and psoriasis patients (PSO) of comparable age were also recruited in the study cohort 2.

As expected, the results of metabolomics analysis on the study cohort 2 largely conform to the previous observations in study cohort 1. In sPLS-DA, PC group was between PSO and CV groups and apparent separation was achieved among the four groups (Fig. 4a). 25 differential metabolites identified in PSO/CON comparison in the study cohort 1 were demonstrated to be significantly as well in the PSO, CV and PC groups comparing to CON group in the study cohort 2 (Fig. 4b, c). Although all identified LPLs were upregulated in PSO and PC groups of two study cohorts, LPCs levels were even higher in PC group compared PSO group (Fig. 4d). In the study cohort 2, the aforementioned LPC (22:5), LPC (20:3) and GPC not only drastically increased in PSO group, but also had higher levels in PC group. Although all the identified LPIs upregulated in the PSO group of two study cohorts, psoriasis patients with coronary heart diseases had significant lower levels (Fig. 4d).

The dysregulated trends of DAs in patients of study cohort 2 were also consistent with the results of study cohort 1, but there were no significant changes between PSO and PC groups (Fig. 4c, d). Considering that DAs levels were inversely correlated with psoriasis area and severity index in study cohort 1, this outcome was beyond our expectations. The results of metabolic profiling in study cohort 1

had demonstrated acyl-carnitines, a critical carrier in fatty acid oxidation, decreased in the psoriasis patients. In study cohort 2, although middle-chain acetyl-carnitines decreased in all patients, no significant changes were found between PSO and PC groups, which was consistent with the results of DAs.

Although only six individuals in PC group were treated with Ixekizumab, the changes of lipids metabolism conformed to the previous observations in study cohort 1. After Ixekizumab treatment, LPLs, DAs and acyl-carnitines were ameliorated to normal levels in psoriasis patients with coronary heart diseases (Fig. 5). This result indicated that IL-17A mAb might restore the dysregulated lipids metabolism to normal level in psoriasis patients with coronary heart diseases.

4. Discussion

In this study, metabolic analysis was conducted in two study cohorts including healthy people, before and after Ixekizumab treated psoriasis patients and psoriasis patients with coronary heart diseases. In the discovery of study cohort 1, majority of identified differential metabolites were attributed to LPCs which was regarded as a second messenger involved in pro-inflammatory effects in both psoriasis and atherosclerosis (AS) [25, 26]. Monocytes stimulated by LPCs can produce IL-1β to further activated T lymphocyte to secrete IL-17A, which was the important pathogenic factor in psoriasis [27]. In addition, LPCs had a direct effect on immunocytes including monocyte, macrophages and T-lymphocytes [28–30]. Meanwhile, IL-17A produced by stimulated T-lymphocyte might also induce macrophage lipid uptake, which was a critical step in the pathophysiology of AS[31]. Obviously, cumulated literatures emphasized high blood concentration of LPCs was a risk factor for psoriasis and CVDs. LPIs, as another LPL identified in this study had the similar trend. LPIs was one of the ligands of GPR55, which was detected in many immune organs, such as spleen, thymus and blood immune cells[32]. Natural killer cells (NK cells) and monocytes activated by GPR55 can produce proinflammatory factors such as IL-12 and TNF-α, which have critical roles in pathogenesis of psoriasis and CVDs[33]. Elevated LPIs also were reported in a quantitative profiling of high-fat diet apolipoprotein E-deficient mice research, compared with other LPLs, LPIs continuously increased with worsening of AS, which were considered as stably biomarkers of AS[34]. Due to activation of GPR55 by LPIs can cause intracellular overload and increase calcium release to accelerate vascular calcification, elevated LPIs was regarded as one of the triggers of AS[34].

DAs and acyl-carnitines significantly decreased in psoriasis patients with or without coronary heart diseases in two study cohorts. In the large-scale metabolic profiling study, acyl-carnitines were considered as the independently factor associated with mortality of cardiovascular events[35]. Azelaic acid (AzA), one of DAs, has anti-inflammatory, antioxidative and antibacterial effects, which has been a medication for the treatment of acne vulgaris[36]. It's also reported AzA had the anti-atherosclerosis effect. In a study of low density lipoprotein receptor knockout mice, in which addition of AzA in the diet of mice can significantly decrease atherosclerotic lesions [37].

As mentioned previously, after 12-week treatment of Ixekizumab, blood levels of those most significantly altered lipidic metabolites such as LPCs, LPIs and DAs in psoriasis patients were restored to a comparable status of Con group. In addition to those reported in psoriasis patients, dysregulated lipids metabolism especially LPLs was considered as the critical pathogenic factor in the progression of CVDs [38]. These results highlight that the treatment of IL-17A mAb can not only ameliorate the lesions of psoriasis, but also restore the dysregulated lipids metabolism to normal level in psoriasis patients.

5. Conclusion

This metabolomics analysis regarding lipids metabolism revealed the identified differential metabolites in psoriasis patients were also significantly dysregulated in psoriasis patients with coronary heart diseases and most of them could be restored after receiving treatment of IL-17A mAb. Since dysregulated lipids metabolism has been regarded as the critical factor of CVDs, the recovery of lipidic profiling in psoriasis patients indicated that IL-17A mAb might have potential protective effect on CVDs, which was worth further evaluation on the therapeutic effect of IL-17A mAb on both psoriasis and CVDs in terms clinical manifestation and pathological changes.

Abbreviations

AzA: Azelaic acid; AUC: area under the curve; CON: healthy people group; CVDs: cardiovascular diseases; CV: coronary heart diseases patients without psoriasis group; DAs: dicarboxylic acids; FFAs: free fatty acids; GPC: glycerophosphocholine; IL-17A mAb: interleukin-17A monoclonal antibody; IXE: Ixekizumab treated psoriasis patients group; LPLs: lysophospholipids; LPAs: lysophosphatidic acids; LPCs: Lysophosphatidylcholines; LPIs: lysophosphatidylinositols; NK cells: Natural killer cells; OPLS-DA: orthogonal partial least squares discrimination analysis; PCA: principal component analysis; PC: psoriasis patients with coronary heart diseases group; PSO: psoriasis patients group; QCs: Quality control samples; ROC: Receiver operating characteristic; sPLS-DA: sparse partial least squares discriminant analysis; UPLC-MS: ultra-performance liquid chromatography mass spectrometry; VIP: variable importance in projection.

Declarations

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Authors' contributions

Conceptualization: ZJ, LX and YYQ; Methodology: CH, SSM and LYC; Clinical samples collection: YQ, CLH and HMY; Data acquisition and analysis: CH, GXY and SSM; Writing-original draft preparation: CH and YQ; Writing-Review and Editing: SSM, LYC and ZJ.

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Availability of data and materials

The datasets used or analyzed in this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the ethics committee of Ruijin Hospital Shanghai Jiao Tong University. Written informed consent was obtained from all participants.

Competing interests

All authors declare that there are no conflicts of interest.

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Figures

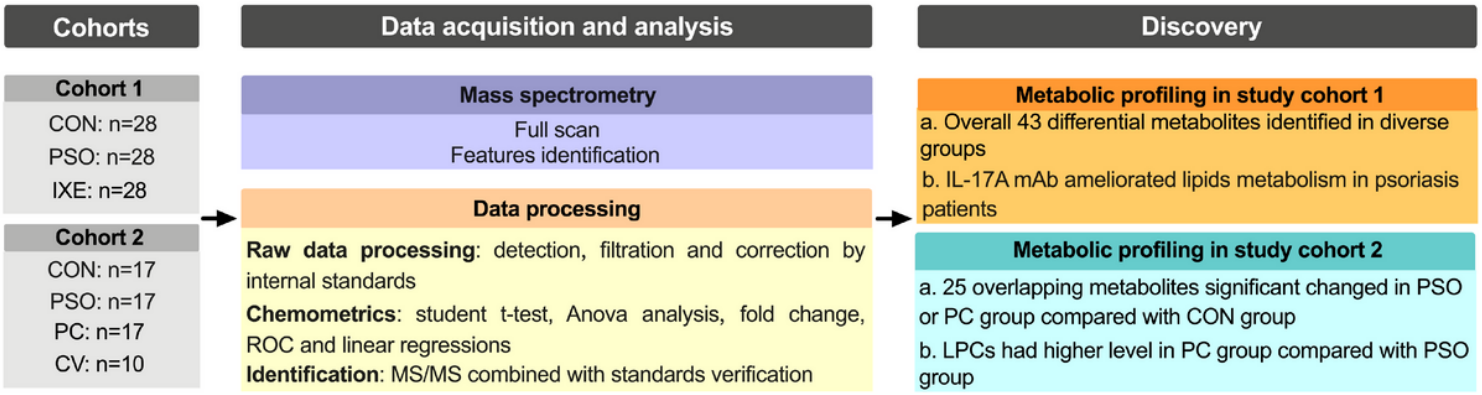
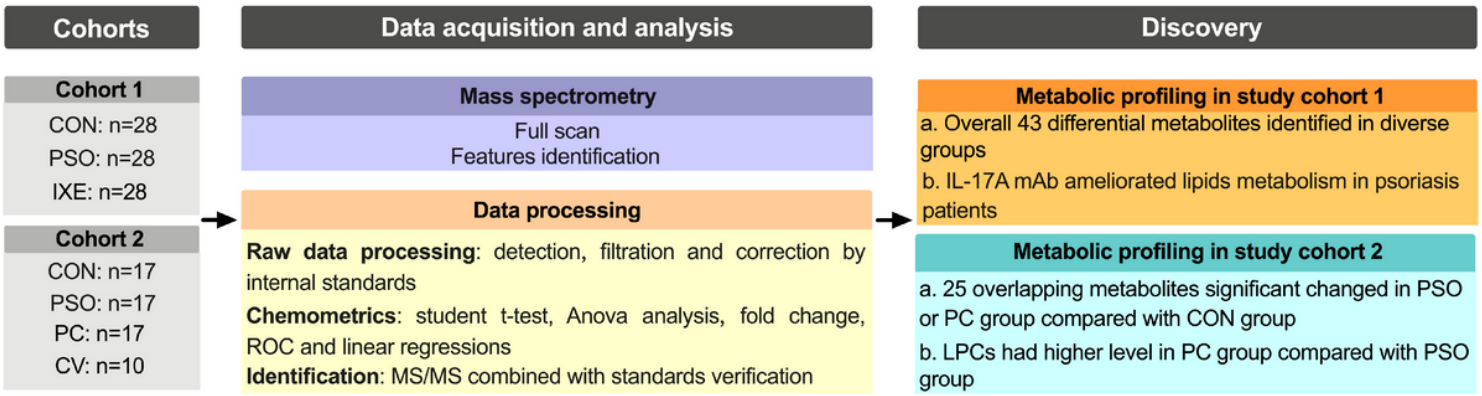


Figure 1

Workflow of this study



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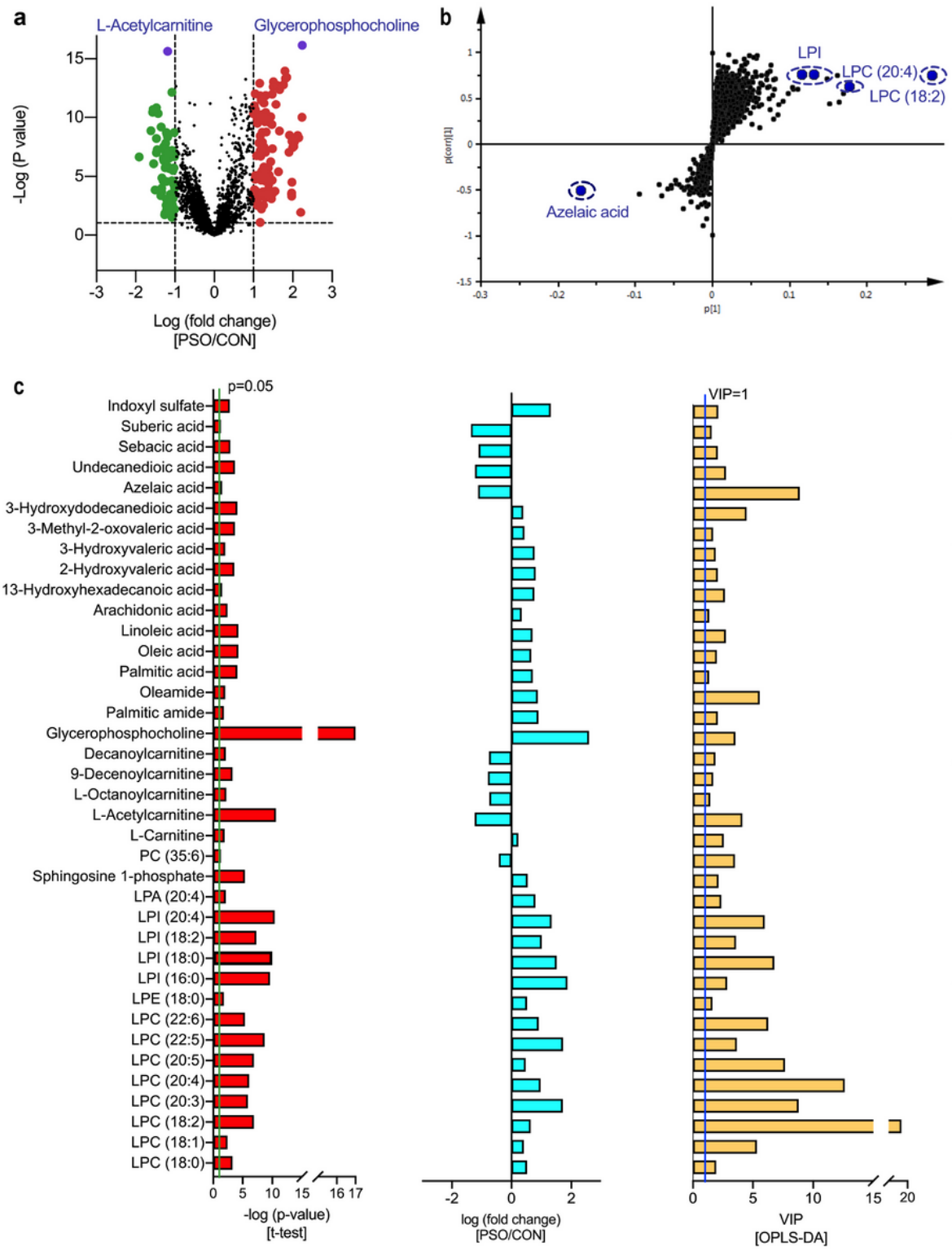
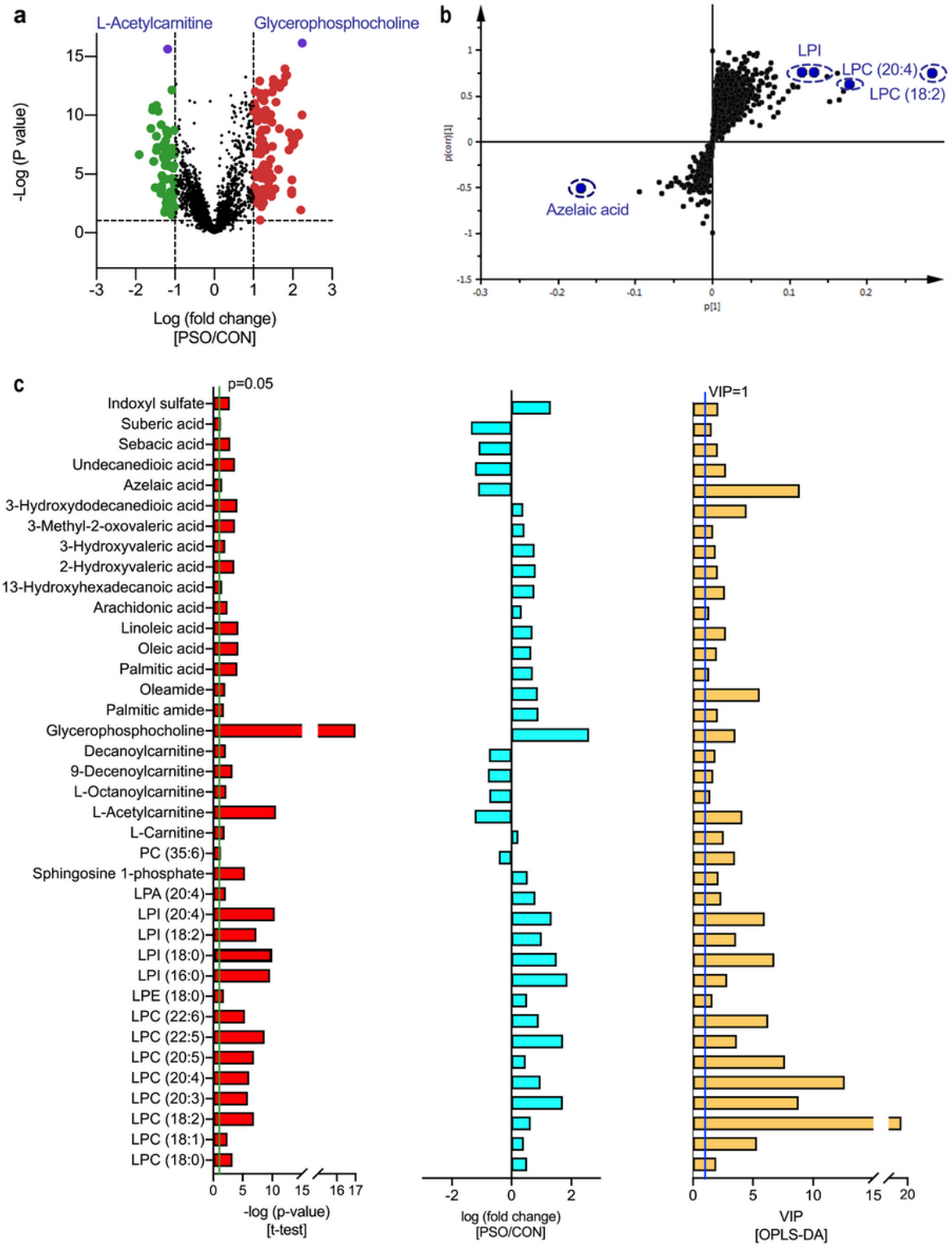


Figure 2

Screen criteria for identified differential metabolites in the PSO/CON comparison in the study cohort 1. a. Volcano plot represents the variation of metabolites in the comparison of PSO/CON group according to the -log(p-value). b. Score plots for covariance and reliability correlation from OPLS-DA in the PSO/CON comparison. c. 37 identified differential metabolites in the PSO/CON comparison. Bar plots represent, from left to right, −log(p-value) of t-test, fold change and VIP values obtained from OPLS-DA.



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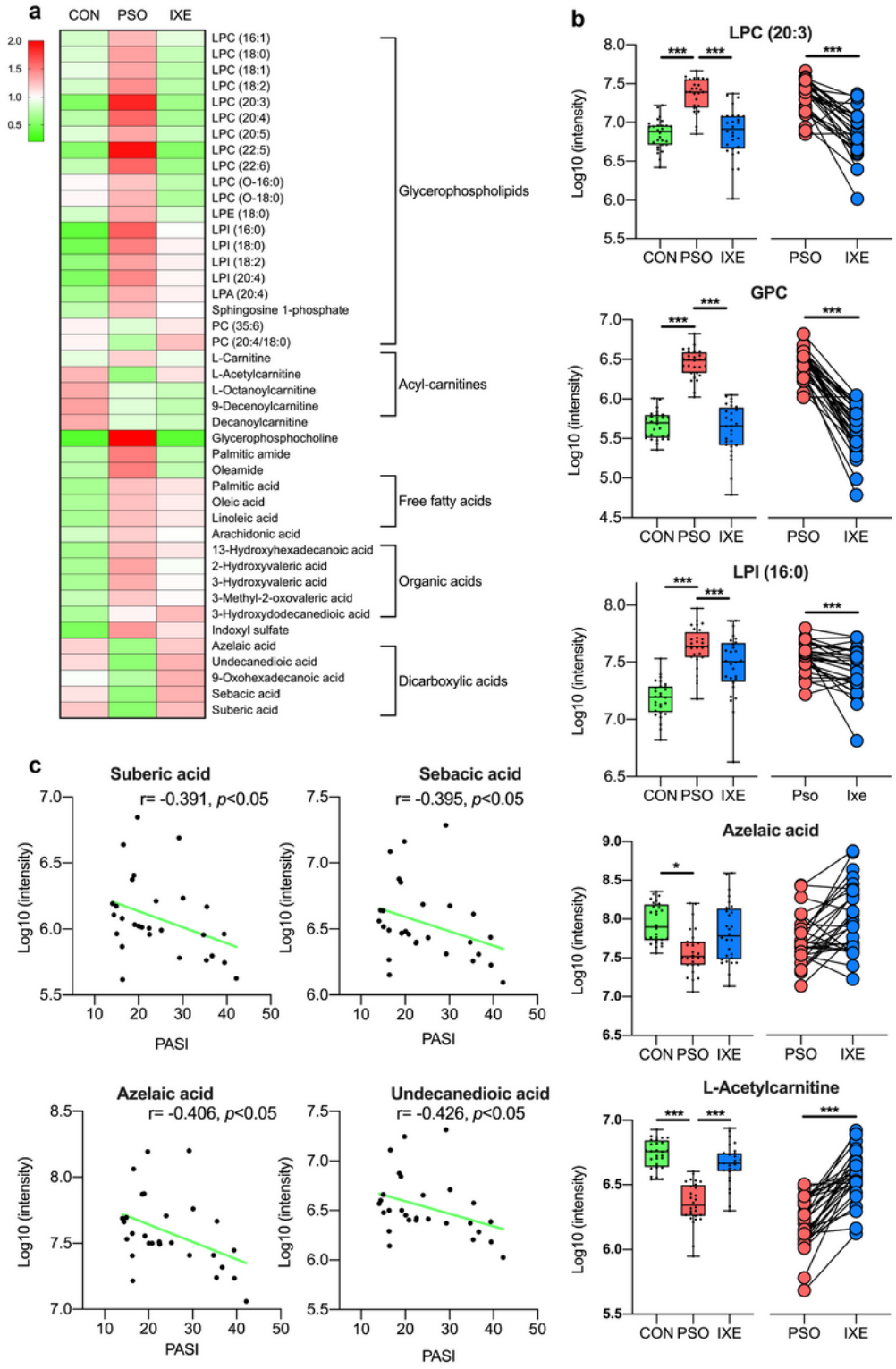

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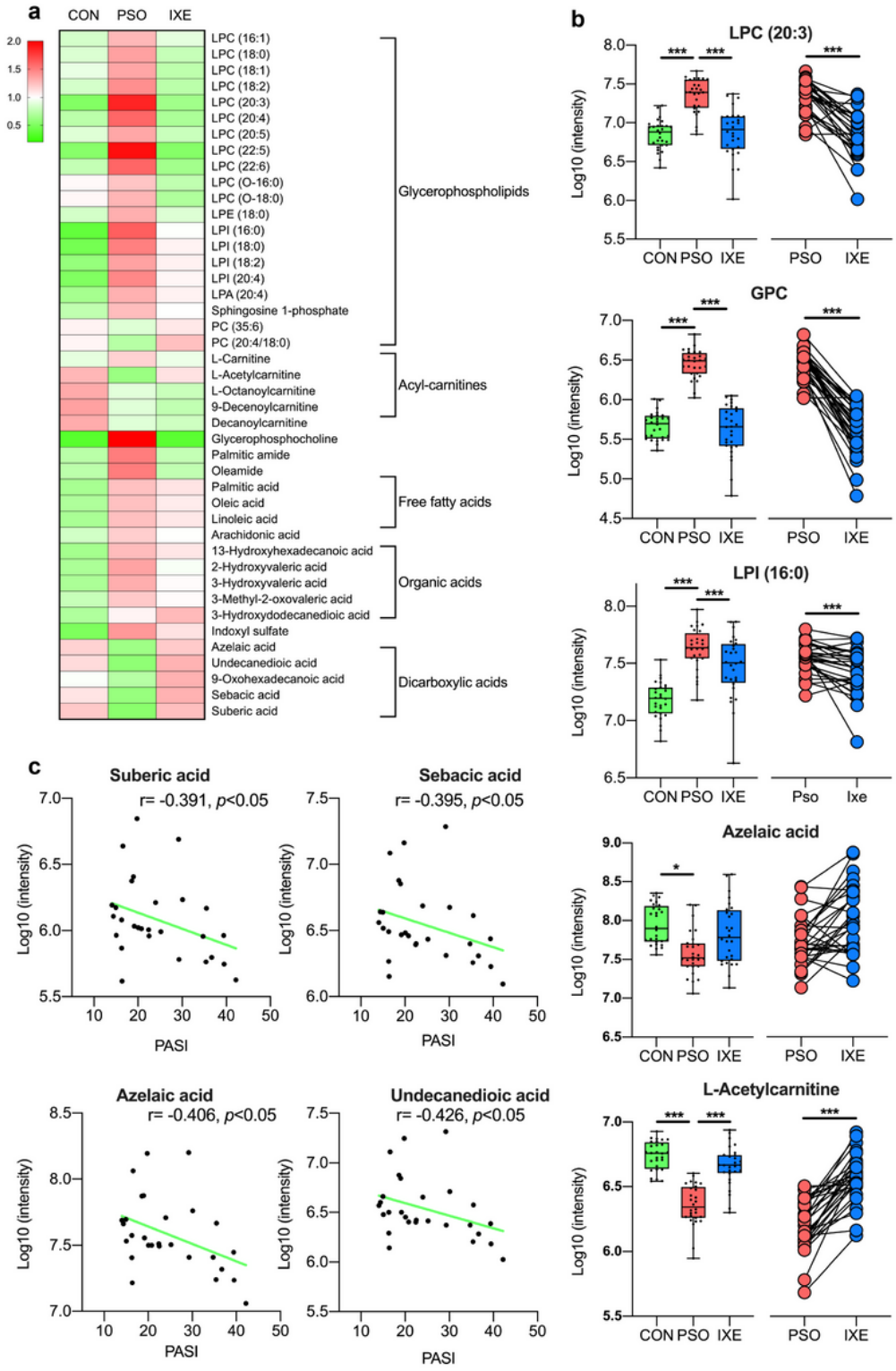

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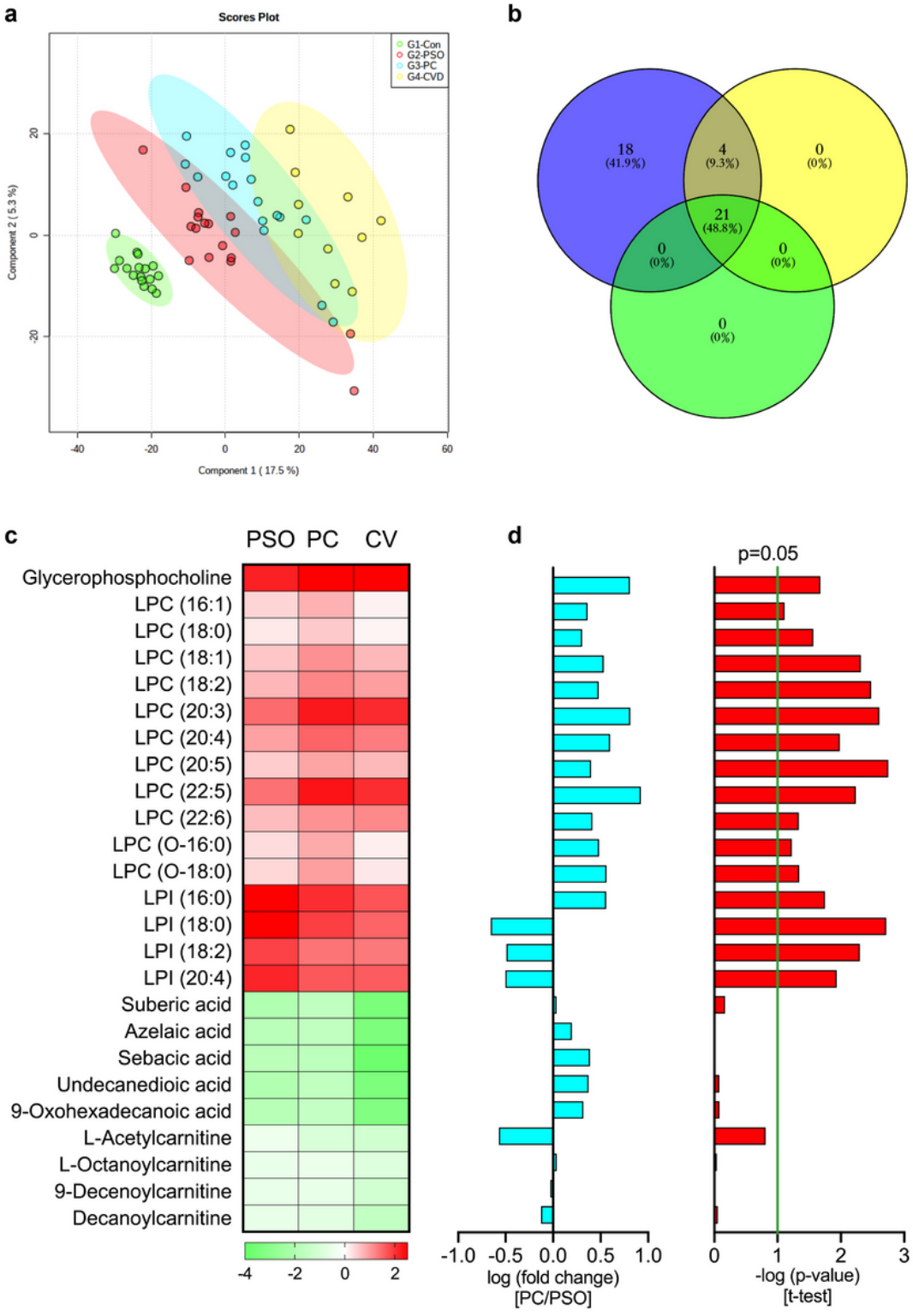

Figure 4

Common and specific metabolites in psoriasis patients with or without coronary heart diseases. a. sPLS-DA score plots of CON, PSO, PC and CV groups in the study cohort 2. CON group is labelled by green cycles, PSO group by red cycles, PC group by blue cycles and CV group by yellow cycles. b. Venn diagram of overlapping 25 metabolites in the PSO, CV and PC groups compared with CON group in the study cohort 2. c. Heatmap of overlapping 25 metabolites in PSO, PC and CV groups (all compare with the CON

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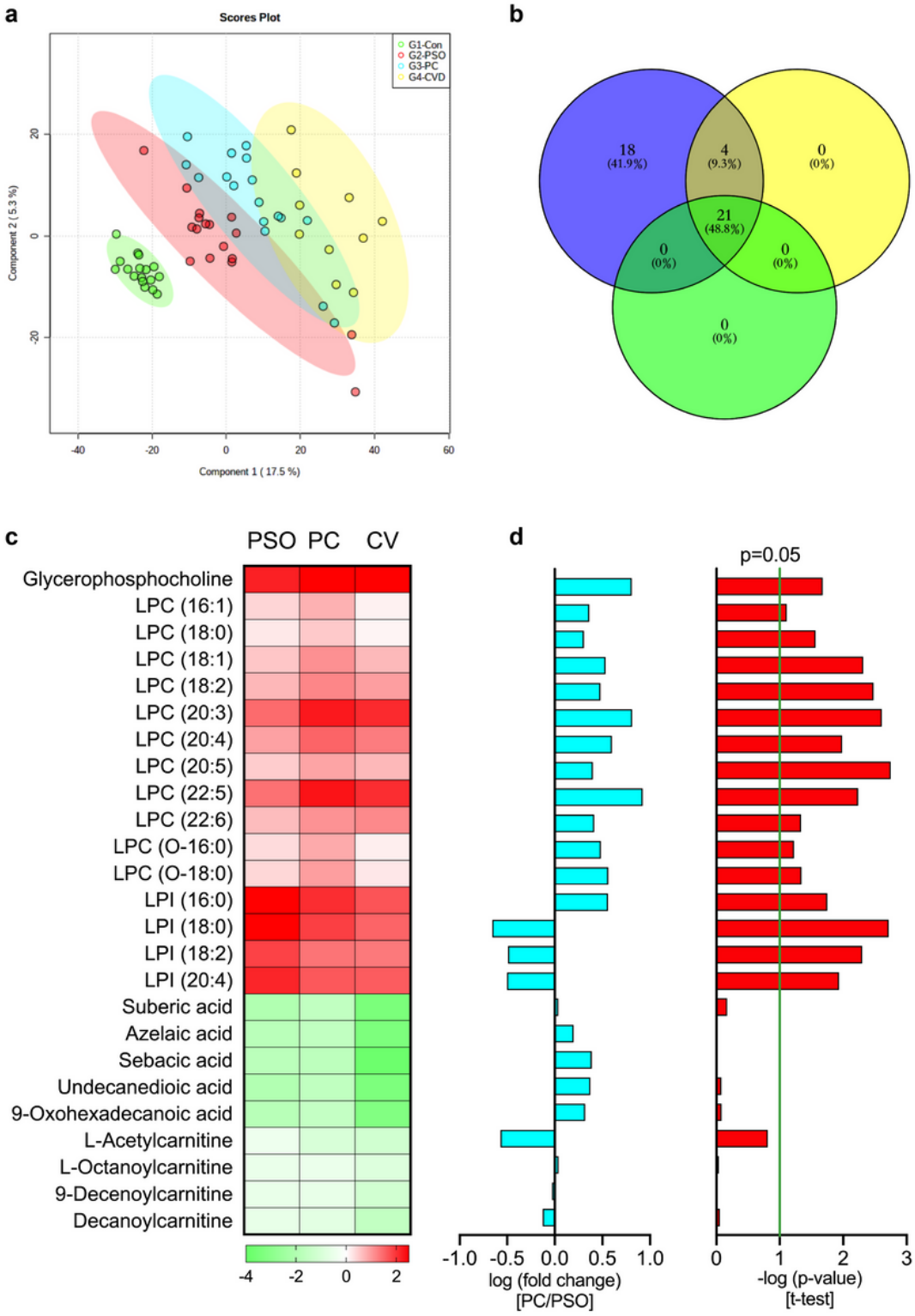

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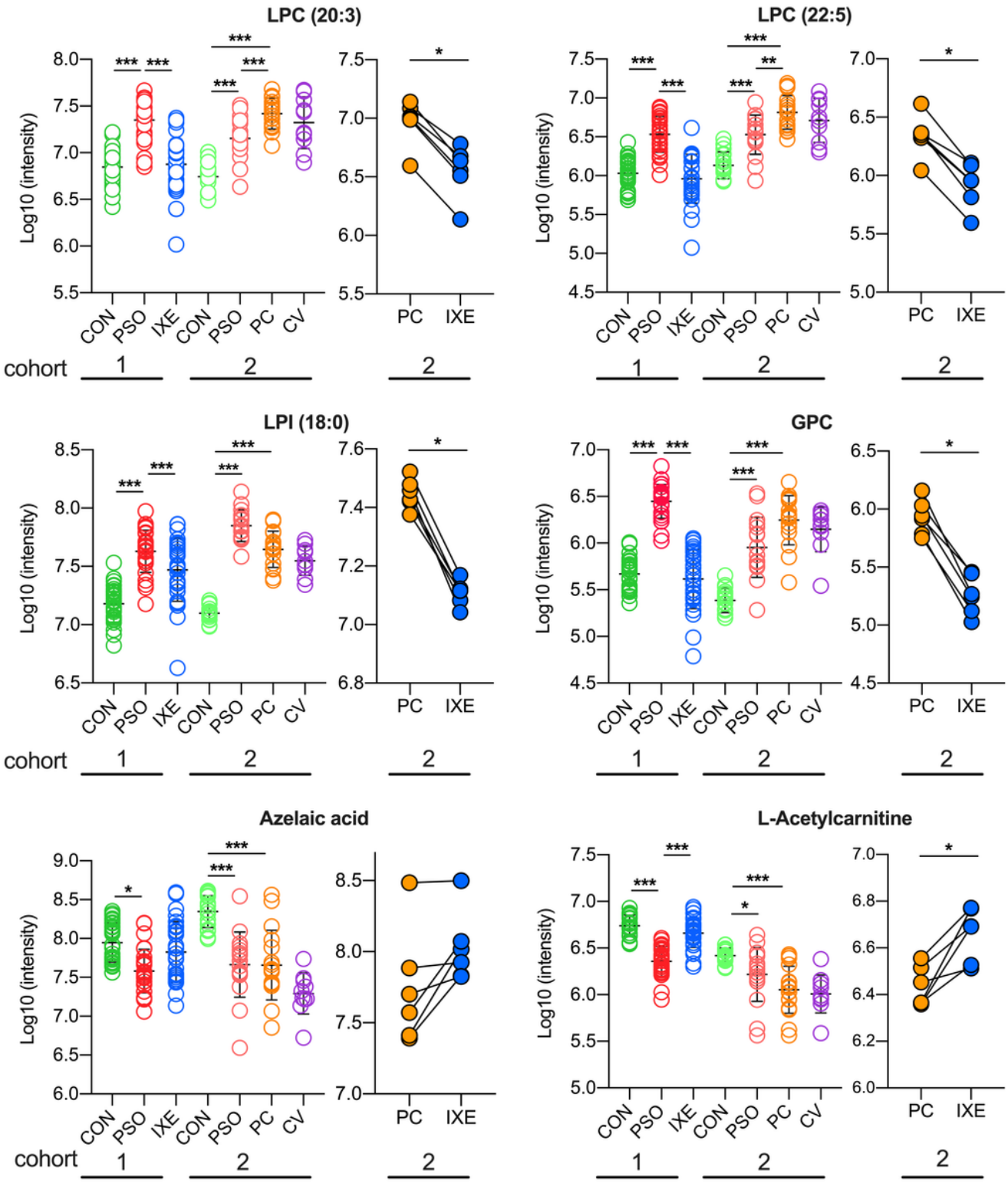
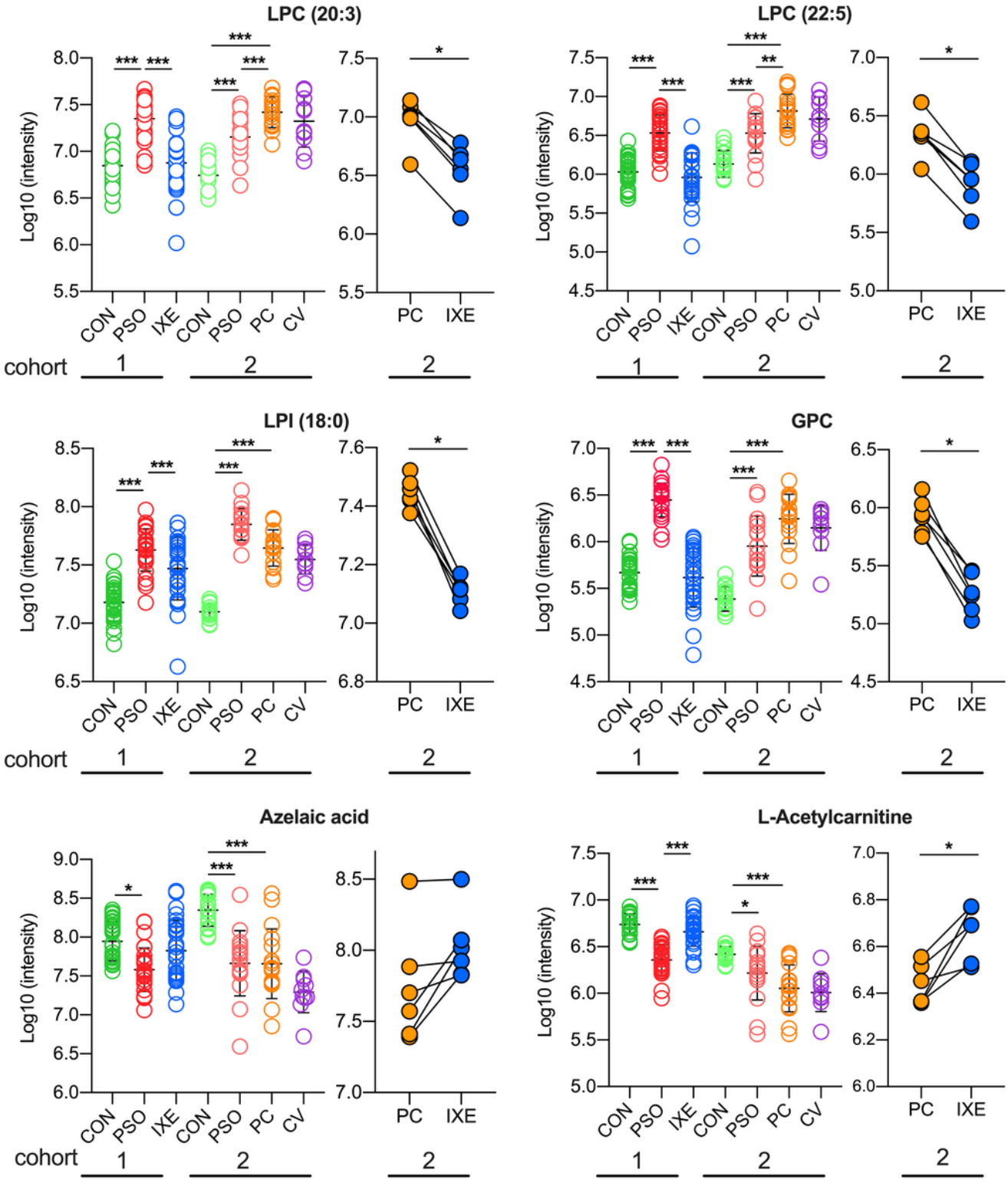


Figure 5

Scatter plots of highlighted metabolites in the study cohorts 1 and 2. Metabolic changes of six Ixekizumab treated individuals from PC group in the study cohort 2 were conformed to the previous observations in study cohort 1. Values are reported as mean ± SD. *p <0.05, **p <0.01, ***p <0.001.



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