

Original Research

Multi-Omics Analysis Uncovers a Link Between Dysregulated Steroid Hormone Biosynthesis and Pediatric IgA Vasculitis Nephritis

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Academic Editor: Graham Pawelec

Submitted: 19 May 2026 Revised: 10 August 2026 Accepted: 31 August 2026 Published: 14 October 2026

Abstract

Background: IgA vasculitis (IgAV) is a systemic vasculitis with variable clinical manifestations, ranging from self-limiting cutaneous purpura and joint pain to severe gastrointestinal and renal involvement. However, whether specific metabolites are associated with these heterogeneous clinical manifestations remains unclear. This study aimed to identify metabolic and proteomic signatures associated with distinct clinical manifestations of IgAV, particularly IgAV nephritis (IgAVN), and to identify molecular features potentially associated with disease pathogenesis. **Methods:** We performed liquid chromatography–tandem mass spectrometry (LC–MS/MS)-based metabolomic and exploratory proteomic analyses of plasma samples from patients with IgAV with isolated cutaneous purpura or additional joint, gastrointestinal, or renal involvement and from healthy controls. **Results:** Metabolomic analysis revealed significant differences between patients with IgAV, including those with IgAVN, and healthy controls. A total of 65 differentially abundant metabolites were identified, with the steroid hormone biosynthesis pathway among the most prominently altered pathways. Notably, patients with IgAVN exhibited a distinct metabolomic profile compared with patients without renal involvement. Levels of six steroids and steroid metabolites, including tetrahydrocorticosterone, tetrahydrocortisone, cortisone, aldosterone, androsterone glucuronide, and progesterone, decreased in patients with IgAVN compared with healthy controls. Proteomic profiling identified 50 upregulated and 12 downregulated proteins in patients with IgAV compared with healthy controls, with enrichment of pathways related to platelet activation and complement and coagulation cascades. Compared with healthy controls, 33 upregulated and 154 downregulated proteins were identified in the IgAVN group. Additionally, IgAVN was associated with a distinct proteomic signature involving the intestinal immune network, B cell receptor signaling, and cholesterol metabolism. Decreased levels of steroids and steroid metabolites were significantly associated with alterations in immunoglobulins and coagulation factors identified by exploratory proteomic analysis. **Conclusions:** Integrated metabolomic and proteomic analyses identified distinct molecular signatures associated with IgAV and IgAVN. Decreased levels of steroids and steroid metabolites and alterations in immune response, coagulation, and lipid metabolic pathways were particularly associated with IgAVN. These findings provide insights into the molecular features associated with IgAV and identify candidate biomarkers of disease severity and potential therapeutic targets that warrant further investigation.

Keywords: IgA vasculitis; IgA vasculitis nephritis; steroid hormone biosynthesis; metabolomics; proteomics; apolipoprotein; intestinal IgA network

1. Introduction

IgA vasculitis (IgAV), also known as Henoch-Schönlein purpura (HSP), is a systemic small-vessel vasculitis characterized by the deposition of IgA-containing immune complexes in various organs [1]. The disease primarily affects children, though adults are also susceptible [2,3]. The clinical presentation of IgAV is heterogeneous, ranging from self-limiting cutaneous purpura and joint pain to severe gastrointestinal and renal involvement [4,5]. In particular, IgA vasculitis nephritis (IgAVN) represents a

major concern due to its potential to progress to chronic kidney disease and end-stage renal failure [6]. The pathogenesis of IgAVN is complex and not fully understood, but is presumed to involve a combination of genetic predisposition, environmental factors, and immune dysregulation [2]. Specifically, aberrant glycosylation of IgA1 has been implicated in the pathogenesis of IgA deposition in the kidneys in patients with IgAVN [7,8].

Recent advances in omics technologies, such as metabolomics and proteomics, have opened new avenues for exploring the complex molecular mechanisms under-



lying kidney diseases [9]. Metabolomics allows for the comprehensive assessment of small molecular metabolites in biological samples from pediatric nephrotic syndrome, providing insights into the metabolic state of an organism and its response to disease [10]. Proteomics, on the other hand, enables the identification and quantification of proteins, offering a snapshot of the functional activity within cells and tissues [11]. Several studies have explored the metabolomic landscape of IgAV and IgAVN [12]. Specifically, altered amino acid metabolism and lipid dysregulation have been implicated in IgAV pathogenesis [12]. While metabolomics has revealed biomarkers for IgAV severity, proteomics has provided key insights into IgAVN pathophysiology [10,11,13,14].

Despite these advancements, significant knowledge gaps remain. Most proteomic and metabolomic studies in IgAV have focused on analyzing either metabolites or proteins separately, and a holistic understanding of the interplay between the metabolome and proteome in IgAV and IgAVN is still lacking. Moreover, there is a paucity of studies that compare the metabolomic and proteomic profiles of IgAV patients with varying degrees of disease severity, particularly those that focus on specific features of IgAVN. The relationship between identified omics changes and histopathological findings also requires further exploration.

In this study, we performed a comprehensive, integrated metabolomic and proteomic analysis on samples obtained from IgAV patients with varying disease severity. Metabolomics revealed distinct metabolite profiles among IgAV patients based on organ involvement. Notably, IgAVN patients exhibited a unique metabolomic signature characterized by a significant reduction in six steroid hormones compared to healthy controls, suggesting a potential role of decreased steroid biosynthesis in IgAV/IgAVN pathogenesis. Furthermore, proteomic analysis identified a distinct protein expression pattern in IgAVN patients compared to both non-nephritic IgAV patients and healthy controls. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis of differentially expressed proteins in IgAVN showed significant enrichment in pathways related to the intestinal immune network, B cell receptor signaling, and cholesterol metabolism. Network analysis identified a functional module comprised of complement and coagulation cascades, apolipoproteins, and vitamin metabolism within the differentially expressed proteins of IgAVN patients. Importantly, correlation analysis demonstrated a significant association between these differentially expressed proteins and reduced steroid hormones in IgAVN patients, further supporting the hypothesis that dysregulation of steroid biosynthesis contributes to the pathogenesis of IgAVN. These integrated metabolomic and proteomic findings provide a systems-level understanding of IgAV/IgAVN pathogenesis and offer potential rationales for targeted therapeutic interventions.

2. Materials and Methods

2.1 Participants

Inclusion of participants: Patients aged 2 to 14 years who met the international consensus criteria for IgA vasculitis (IgAV) were recruited [15]. These patients were first diagnosed and treated between February 2018 and February 2020 at the Department of Pediatric Nephrology, the Second Hospital & Clinical Medical School, Lanzhou University. Based on their clinical manifestations, the patients were divided into four groups, with 20 patients per group: (1) Patients with cutaneous purpura alone, without involvement of other organs (designated as the cutaneous group hereinafter); (2) Patients presenting with cutaneous purpura and joint pain, but without gastrointestinal or renal involvement (designated as the joint group); (3) Patients with cutaneous purpura and gastrointestinal symptoms such as abdominal pain, occult blood, or bloody stools, but without joint or kidney involvement (designated as the GI group); (4) Patients with IgA vasculitis nephritis (IgAVN), without joint or digestive system involvement (designated as the IgAVN group). The diagnosis of IgAVN was based on the international consensus and characterized by hematuria, proteinuria, abnormal renal function, and IgA deposition in kidney biopsy [15]. In the control group, 20 age- and gender-matched healthy volunteers were recruited from the Children's Health Management Center of the Second Hospital & Clinical Medical School, Lanzhou University. The clinical characteristics of all participants were shown in the Table 1.

Exclusion criteria: Patients with hepatitis, primary acute or chronic nephritis, diabetes mellitus, systemic lupus erythematosus, cancer, endocrine disorders, and cirrhosis were excluded.

2.2 Sample Collection

Blood samples were collected from all patients prior to receiving treatment after a 12-hour fasting period. Blood samples for healthy volunteers were collected after a 12-hour fasting period. Plasma was obtained by centrifugation at 3000 rpm for 20 minutes at 4 °C, and the supernatant was aliquoted and stored at –80 °C.

2.3 Ultraperformance Liquid Chromatography and Mass Spectrometry

Plasma metabolites were extracted from 100 µL of plasma by mixing with 80% pre-cooled methanol on ice for 5 minutes. Following centrifugation, the supernatant was diluted to 53% methanol for liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis. Chromatographic separation was performed using an Agilent 1290 UPLC system (Agilent, Beijing, China) with a UPLC HSST3 column at 40 °C. Samples were analyzed in randomized order, with running of quality controls every ten tests. The mobile phases contained 0.1% formic acid and acetonitrile for positive ion mode, while 10 mM ammonium

Table 1. The baseline characteristics and initial clinical data for participants.

	IgAV with organ involvement of					
	IgAVN (n = 20)	GI (n = 20)	Joint (n = 20)	Cutaneous (n = 20)	Healthy (n = 20)	<i>p</i> value
Male/Female (n)	14/6	10/10	10/10	12/8	13/7	0.619 [#]
Age (Year)	9.5 ± 2.8	7.7 ± 3.1	8.4 ± 2.3	8.3 ± 2.4	8.1 ± 2.8	0.383 [※]
Hematuria (number of participants in each category)						
—	2	19	20	20	20	<0.0001 ^{\$}
+	1	0	0	0	0	
++	7	1	0	0	0	
+++	10	0	0	0	0	
Proteinuria (number of participants in each category)						
—	3	18	19	20	20	<0.0001 ^{\$}
+	8	1	1	0	0	
++	6	1	0	0	0	
+++	3	0	0	0	0	
Urinary microalbumin (mg/L)	317.0 ± 182.0	26.2 ± 56.3	8.1 ± 7.9	28.1 ± 63.9	ND	<0.0001 [※]
Beta-2-microglobulin (μg/L)	738.9 ± 1325.1	308.5 ± 394.4	326.1 ± 410.5	265.5 ± 345.5	ND	0.209 [※]
Serum creatinine (μmol/L)	47.6 ± 14.5	49.7 ± 16.7	51.0 ± 16.1	53.9 ± 22.6	ND	0.732 [※]
IgA (g/L)	2.33 ± 0.98	2.22 ± 0.86	1.85 ± 0.57	2.06 ± 0.87	ND	0.418 [※]
Complement C3 (g/L)	1.09 ± 0.19	1.19 ± 0.20	0.99 ± 0.22	1.03 ± 0.14	ND	0.061 [※]

[#]Chi-square analysis; ^{**}ANOVA analysis; [§] Chi-square analysis shows a significant difference between IgAVN and other groups (*p* < 0.0001), while no significant difference among other 4 groups. ND, not determined; IgAV, IgA vasculitis; IgAVN, IgAV nephritis; GI, gastrointestinal involvement.

acetate and acetonitrile for negative ion mode. The flow rate was set to 0.4 mL/min, and metabolites were detected using the 6545 Q-TOF mass spectrometer (Agilent).

2.4 Data Analysis

The metabolomic data were analyzed using Compound Discoverer 2.1 to identify and quantify metabolites across different groups. The analysis included peak alignment and quantification of metabolites. To assess differences in metabolite profiles among the groups, principal component analysis (PCA) was used to visualize variance in the data and partial least squares discriminant analysis (PLS-DA) was used to identify differentially expressed metabolites. Differentially expressed metabolites were identified based on variable importance in projection (VIP) values, fold change (FC), and *p*-values from *t*-tests, with thresholds set at VIP >1, FC >2 or <0.5, and *p* < 0.05. Receiver operating characteristic (ROC) curves were generated to assess the discriminatory performance of differentially expressed metabolites in this exploratory study.

2.5 Protein Extraction for Proteomics

Six samples from each group were randomly selected for an exploratory proteomic analysis as previously reported for discovery-phase proteomics [16]. To ensure the representativeness of the selected patient subset, variance homogeneity was assessed using urinary microalbumin levels of patients. The subset (*n* = 6) showed no significant difference in variance compared with the full cohort (*n* =

20) for each group (F-test; *p* = 0.51, 0.15, 0.13, and 0.59 for IgAV with renal, GI, joint, and cutaneous involvement, respectively), supporting their representativeness. Plasma was thawed and high-abundance proteins removed using the ProteoMiner protein enrichment kit (Bio-Rad Laboratories, Shanghai, China). Proteins were lysed using lysis buffer (100 mM ammonium bicarbonate, 8 M urea, 0.2% SDS, pH = 8) through vortex, and subjected to ultrasound in an ice-water bath for 5 minutes to ensure complete lysis. The samples were then centrifuged at 4 °C at 12,000 *g* for 15 minutes, and the supernatant was collected and treated with dithiothreitol (final concentration of 10 mM) at 56 °C for 1 hour followed by a one-hour incubation with iodoacetamide (Sigma-Aldrich, Shanghai, China) at room temperature in the dark. Protein was subsequently precipitated by adding four volumes of pre-chilled acetone under –20 °C for at least 2 hours followed by centrifugation at 12,000 ×*g* for 15 minutes. The precipitate was resuspended and washed with pre-chilled acetone and centrifuged at 12,000 ×*g* for 15 minutes. Finally, the precipitate was air-dried and dissolved in dissolution buffer (6 M urea, 100 mM triethylammonium bicarbonate, pH = 8.5). The protein concentration was determined by Bradford quantification kit (Beyotime Technology, Shanghai, China).

2.6 Proteolytic Digestion and LC–MS/MS Analysis

One hundred twenty micrograms of protein were lysed with 1.5 μg of trypsin in 500 μL of 100 mM triethylammonium bicarbonate buffer at 37 °C for 4 hours to facil-

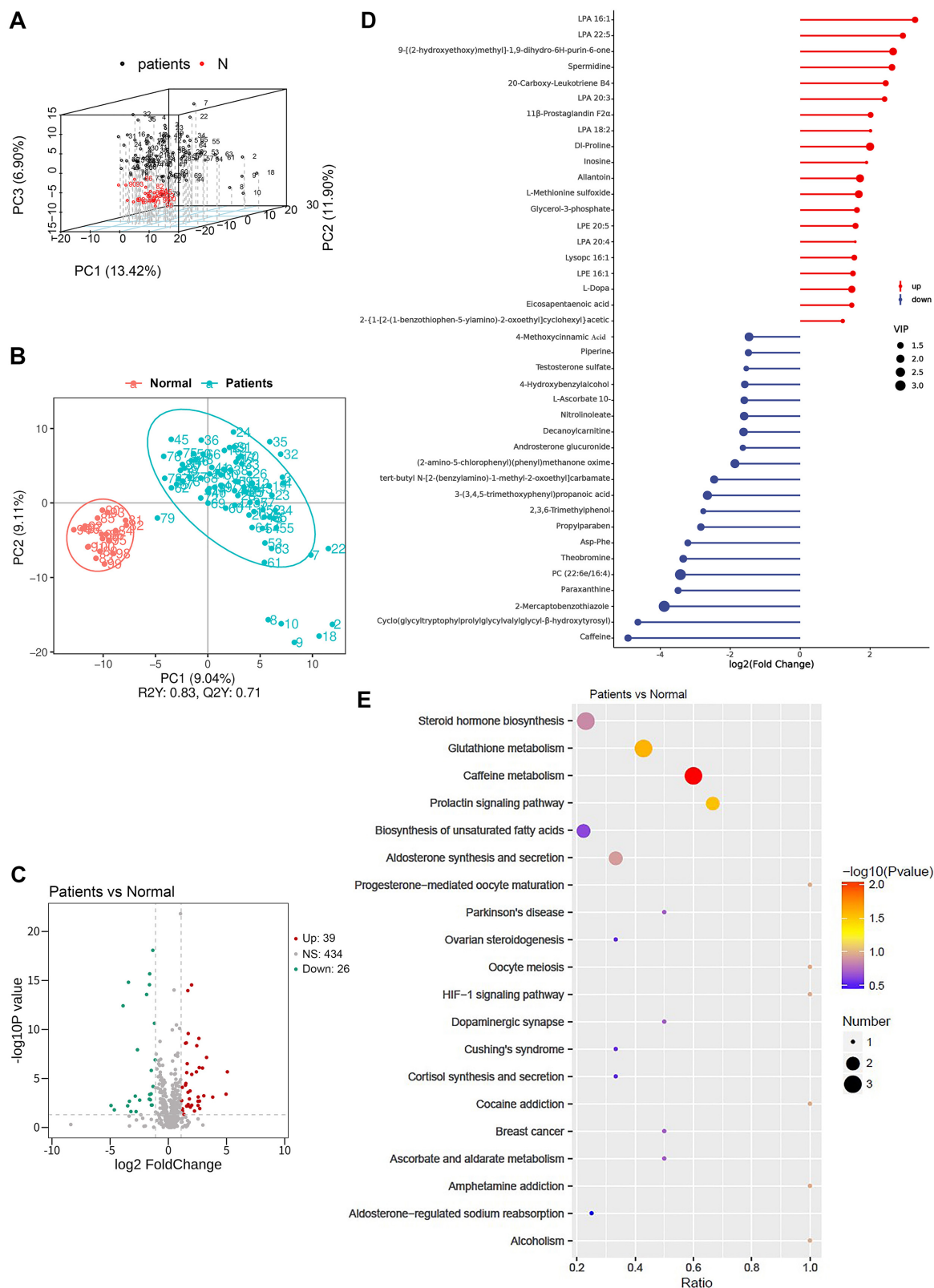


Fig. 1. The metabolomic features of IgAV patients are distinct from normal controls. (A) Three-dimensional PCA plots clearly distinguish IgAV patients from the healthy controls. N represents normal controls. (B) PLS-DA model confirms significant differences in metabolites between IgAV patients and healthy controls. (C) Volcano plots show differential metabolites in IgAV patients compared to healthy controls. (D) Top differential metabolites in IgAV patients compared to healthy controls. (E) Metabolic pathways enriched by KEGG analysis, in which steroid hormone biosynthesis pathway is at the top of these pathways. PCA, principal component analysis; PLS-DA, partial least squares discriminant analysis; KEGG, Kyoto Encyclopedia of Genes and Genomes.

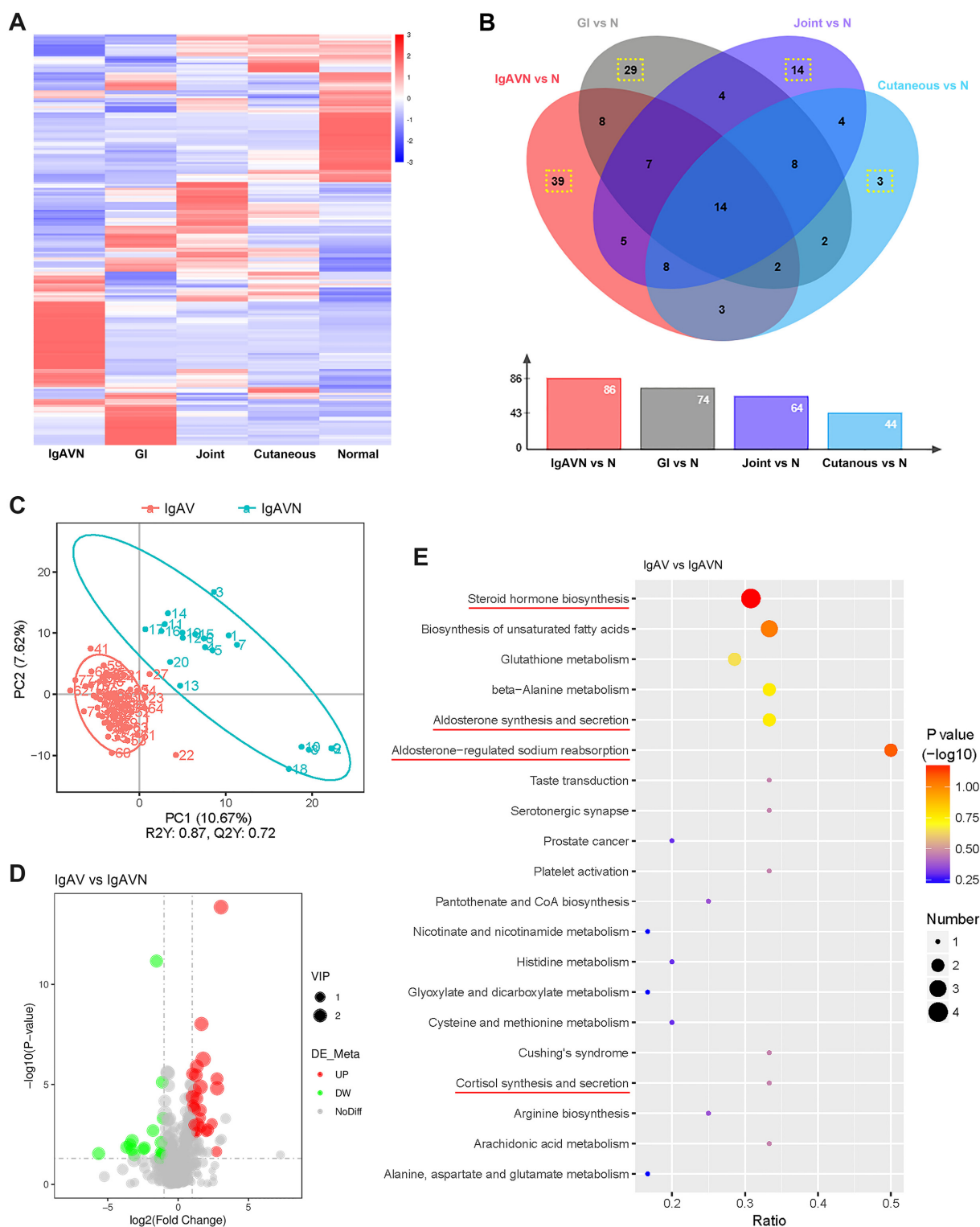


Fig. 2. Plasma metabolomics is associated with clinical manifestations of IgAV and IgAVN. (A) Heatmap shows distinct metabolic profiling of IgAV patients with different organ involvement. (B) Venn diagram shows the number of differentially expressed metabolites in IgAV patients with different organ involvement compared to healthy controls. The number of differentially expressed metabolites varies based on the clinical manifestation in IgAV patients, with the most in IgAVN patients and the least in the patients with cutaneous involvement only. (C) Partial least squares discriminant analysis (PLS-DA) for IgAVN and IgAV patients. (D) Volcano plots show differentially expressed metabolites in IgAV patients compared to IgAVN patients. (E) Top pathways enriched by KEGG analysis in the comparison between IgAV and IgAVN patients. Steroid hormone biosynthesis pathway is significantly enriched.

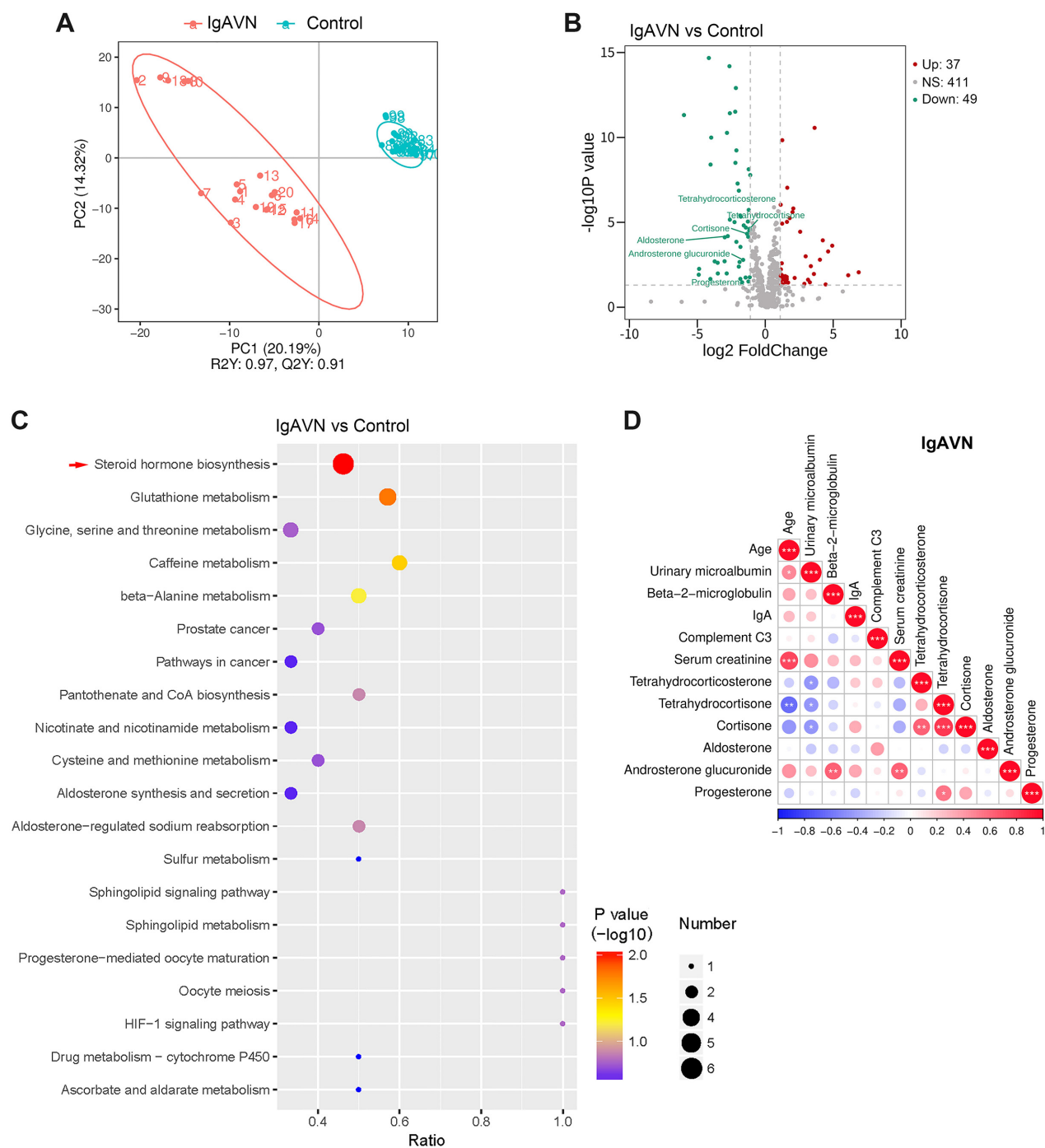


Fig. 3. Unique metabolomic profile of IgAVN patients. (A) Partial least squares discriminant analysis (PLS-DA) for IgAVN patients and healthy controls. (B) Volcano plots show differentially expressed metabolites in IgAVN patients compared to healthy controls. Levels of six steroids are significantly reduced in IgAVN patients. (C) Top pathways enriched by KEGG analysis in IgAVN patients compared to healthy controls. Steroid hormone biosynthesis pathway is significantly enriched (red arrow). (D) Correlation analysis between downregulated steroids and clinical data of IgAVN patients. Red: positive correlation; blue: negative correlation. * $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$.

itate enzymatic digestion. The protein digest was further digested by adding another 1.5 μg of trypsin and CaCl_2 for overnight enzymatic digestion. The reaction was terminated with formic acid, followed by centrifugation at 12,000

$\times\text{g}$ for 5 min at room temperature. The supernatant was subjected to desalting and washing on a C18 cartridge. Subsequently, the peptides were eluted with elution buffer containing 0.1% formic acid and 70% acetonitrile, followed by

lyophilization. The peptides were dissolved in 0.1% formic acid solution and subjected to LC–MS/MS analysis. Liquid chromatography was performed using an EASY-nLC 1200 System (Thermo Fisher Scientific, Shanghai, China) and the mass spectrometric analysis was performed on a Q Exactive™ HF-X mass spectrometer equipped with a Nanospray Flex™ ion source (Thermo Fisher Scientific).

2.7 Protein Identification and Quantification

Proteins were identified and quantified using Proteome Discoverer 2.2 (Thermo Fisher Scientific). Mass spectrometry data were searched against the UniProt database (<https://www.uniprot.org/>). Peptide-spectrum matches (PSMs) were filtered to maintain a false discovery rate (FDR) of $\leq 1\%$ using the Percolator algorithm [17], with at least one unique peptide match. For data-independent acquisition (DIA) analysis, Spectronaut (Biognosys, Newton, USA) was used to quantify proteins based on a spectral library generated from the Proteome Discoverer results. Peptide and protein quantification was based on the area under the curve (AUC) of extracted ion chromatograms, with retention time calibration performed using indexed retention time peptides [18]. Differentially expressed proteins (DEPs) were determined using the Student's *t*-test ($p < 0.05$), with a fold-change threshold of $\log_2\text{FC} > 0.5$.

2.8 KEGG Enrichment Analysis

KEGG analysis was used to identify pathways enriched by differentially expressed metabolites and proteins for metabolomics and proteomics, respectively. A bubble map was created to visualize the enrichment results, indicating the number of differentially expressed metabolites, or proteins, and their statistical significance. Additionally, the web-based platform MetaboAnalyst (<https://dev.metaboanalyst.ca/>) was also used for signaling pathway analysis [19]. The interactive network of signaling pathways was visualized using PathIN (<https://pathin.cing-big.hpcf.cyi.ac.cy>) [20].

2.9 Statistical Analysis

Chi-square test and one-way ANOVA were performed using GraphPad Prism (version 11.0.2) to compare baseline characteristics of participants between groups. Student's *t*-test was used to identify differentially expressed metabolites and proteins between groups. $p < 0.05$ was considered statistically significant for all comparisons. Pearson correlation analysis was used to evaluate the correlations between metabolites and proteins, as well as between steroids and clinical parameters. Additionally, analysis of covariance (ANCOVA) was used to adjust for age and sex as confounding factors when comparing steroids between patients and healthy controls. To account for multiple comparisons in differential expression and correlation analyses, *p*-values were adjusted using the Benjamini-Hochberg false discov-

ery rate (FDR) method, with $q < 0.05$ considered statistically significant. Unless otherwise specified, all statistical analyses were conducted using R (version 4.5.1).

3. Results

3.1 Clinical Characteristics of the Participants

The baseline characteristics and initial clinical data of participants are summarized in Table 1. The age and gender distributions did not significantly differ between groups. Hematuria was present in 90% (18/20) of IgAVN patients, while only one IgAV patient with gastrointestinal involvement exhibited hematuria. All healthy controls were negative for hematuria. Additionally, proteinuria was observed in 85% (17/20) of IgAVN patients, while 95% (57 out of 60) of IgAV patients and all healthy controls showed no proteinuria. Urinary microalbumin levels were significantly higher in IgAVN patients compared to IgAV patients with GI, joint, or cutaneous involvement ($p < 0.0001$ for all comparisons). There were no significant differences in urinary microalbumin levels between IgAV patients with GI, joint, and cutaneous involvement. Finally, the urinary levels of beta-2-microglobulin, serum creatinine, IgA, and complement C3 did not differ significantly between any of the tested groups.

3.2 Distinct Metabolomic Features in IgAV and IgAVN Patients Compared to Healthy Controls

To investigate the metabolic characteristics of IgAV patients with varying clinical manifestations, we performed comparative metabolomic analysis of plasma obtained from 80 IgAV patients with different clinical presentations and 20 healthy controls. PCA revealed a clear separation between the two groups (Fig. 1A): the patient cohort (including both IgAV and IgAVN) exhibited a relatively scattered sample distribution, while the healthy controls showed superior aggregation. Furthermore, PLS-DA confirmed significant differences in the metabolomic profiles between patients and healthy controls (Fig. 1B). Of the 65 plasma metabolites significantly altered in IgAV patients, 39 metabolites were increased and 26 were decreased compared to controls (Fig. 1C,D). KEGG analysis indicated that several signaling pathways were associated with the differentially expressed metabolites, with the steroid hormone biosynthesis pathway ranking among the top enriched pathways. Other significantly enriched pathways included glutathione metabolism, caffeine metabolism, prolactin signaling, unsaturated fatty acid biosynthesis, and aldosterone synthesis and secretion (Fig. 1E). Furthermore, utilizing the LIPID MAPS database (<https://lipidmaps.org>), we annotated nine of the differentially expressed metabolites as steroids (Supplementary Fig. 1). Notably, the clustered heatmap revealed distinct metabolomic signatures in patients with renal involvement (IgAVN), compared to other IgAV patients with cutaneous, joint, or GI involvement (Supplementary Fig. 2).

3.3 Association of Plasma Metabolomics With Clinical Manifestations of IgAV

To further explore the relationship between plasma metabolomics and clinical manifestations of IgAV, we compared metabolomic profiles of patients with various clinical presentations to healthy controls. As noted above, each clinical cohort demonstrated distinct metabolomic features (Fig. 2A). Specifically, the number of uniquely expressed metabolites for clinical phenotype was as follows: 3 for IgAV with cutaneous involvement, 14 for joint involvement, 29 for GI involvement, and 39 for IgAVN (Fig. 2B, upper). Interestingly, the number of differentially expressed metabolites increased with disease severity: 44, 64, 74, and 86 altered metabolites were identified for cutaneous involvement, joint involvement, GI involvement, and IgAVN, respectively (Fig. 2B, lower). These findings suggest that differential metabolite expression may be associated with severity of IgAV, and that plasma metabolites may serve as indicators for disease severity and pathology.

3.4 Unique Metabolomic Profile of IgAVN Patients

We further compared the metabolomics of patients with IgAVN, recognized as the most severe clinical manifestation of IgAV, against other IgAV patients and healthy controls. PLS-DA demonstrated a clear separation of metabolomic profiles for IgAVN patients from those of IgAV patients with GI, joint, and cutaneous involvement (Fig. 2C). In comparison to IgAVN patients, 28 metabolites increased and 17 metabolites decreased in IgAV patients presenting with joint, GI, and cutaneous involvement (Fig. 2D and **Supplementary Fig. 3**). KEGG analysis of these differentially expressed metabolites highlighted steroid hormone biosynthesis, aldosterone synthesis and secretion, and aldosterone-regulated sodium reabsorption as the top enriched pathways (Fig. 2E).

Furthermore, metabolomic profiles of IgAVN patients were distinct from those of healthy controls (Fig. 3A). A total of 49 metabolites were significantly decreased and 37 increased in IgAVN patients compared to healthy controls (Fig. 3B). Notably, six steroid hormones were significantly downregulated in IgAVN patients compared to healthy controls (Fig. 3B). Consistently, KEGG analysis revealed significant enrichment in the steroid hormone biosynthesis pathway, as well as several other steroid-associated pathways in IgAVN patients (Fig. 3C). Correlation analysis in IgAVN patients showed that, among the downregulated steroids, tetrahydrocortisone was negatively correlated with both age and urinary microalbumin, whereas tetrahydrocorticosterone and cortisone were negatively correlated with urinary microalbumin only (Fig. 3D). In contrast, androsterone glucuronide, a conjugated androgen metabolite, was positively correlated with both beta-2-microglobulin and serum creatinine in these patients. Collectively, these findings implicate that alterations in steroid hormone levels are closely associated with IgAVN pathology.

3.5 Steroid Hormones are Reduced in IgAVN Patients

We next analyzed the interactive network of these steroid-associated pathways, and demonstrated interactions among these pathways, with the steroid hormone biosynthesis pathway at the center of the network (Fig. 4A). Notably, six differentially expressed metabolites were identified in the steroid hormone biosynthesis pathway: tetrahydrocorticosterone, tetrahydrocortisone, cortisone, aldosterone, androsterone glucuronide, and progesterone (Fig. 4B). All these metabolites were significantly decreased in IgAVN patients compared to healthy controls (Fig. 5A). Furthermore, ROC analyses demonstrated that the AUC of these steroids ranged from 0.772 to 0.927 (Fig. 5B), suggesting their good discriminatory ability as targets that merit further study. Additionally, IgAV patients with GI involvement exhibited significant reductions in androsterone glucuronide, progesterone, and aldosterone (Fig. 5C). Conversely, patients with joint involvement showed significantly reduced levels of tetrahydrocorticosterone, androsterone glucuronide, and progesterone (Fig. 5D). Only tetrahydrocorticosterone levels were diminished in IgAV patients presenting solely with cutaneous purpura (Fig. 5E). Because certain steroid hormones may be affected by age and sex [21], these differentially expressed steroids were analyzed after adjusting for age and sex to eliminate potential confounding effects. As shown in Table 2, most steroids remained significantly decreased in patients compared with healthy controls, with the exceptions of progesterone in IgAVN patients and both androsterone glucuronide and progesterone in IgAV patients with joint involvement. Taken together, these findings suggest that the number and type of decreased steroid biosynthesis are intricately linked to IgAV with distinct clinical manifestations.

3.6 Proteomic Profiling of IgAV and IgAVN Patients

To further investigate the underlying mechanisms of IgAV and IgAVN, we conducted an exploratory proteomic analysis on patient plasma, comparing the results to those from healthy controls. The proteomic profile of IgAV patients—including those with GI and joint involvement or solely with cutaneous purpura—significantly differed from that of healthy controls (**Supplementary Fig. 4A**). In comparison to healthy controls, we identified 50 proteins that were upregulated and 12 proteins that were downregulated in IgAV patients (**Supplementary Fig. 4B**). Subsequent KEGG analysis of these differentially expressed proteins revealed significant enrichment in several pathways that are closely associated with the pathology and clinical presentations of IgAV, such as platelet activation, complement and coagulation cascades, and infection pathways for malaria, human papillomavirus, human T-lymphotropic virus, and herpes simplex virus (**Supplementary Fig. 4C**).

Similarly, the proteomic profiling of IgAVN patients exhibited distinct features compared to those of healthy controls, with one control sample clustering closely with

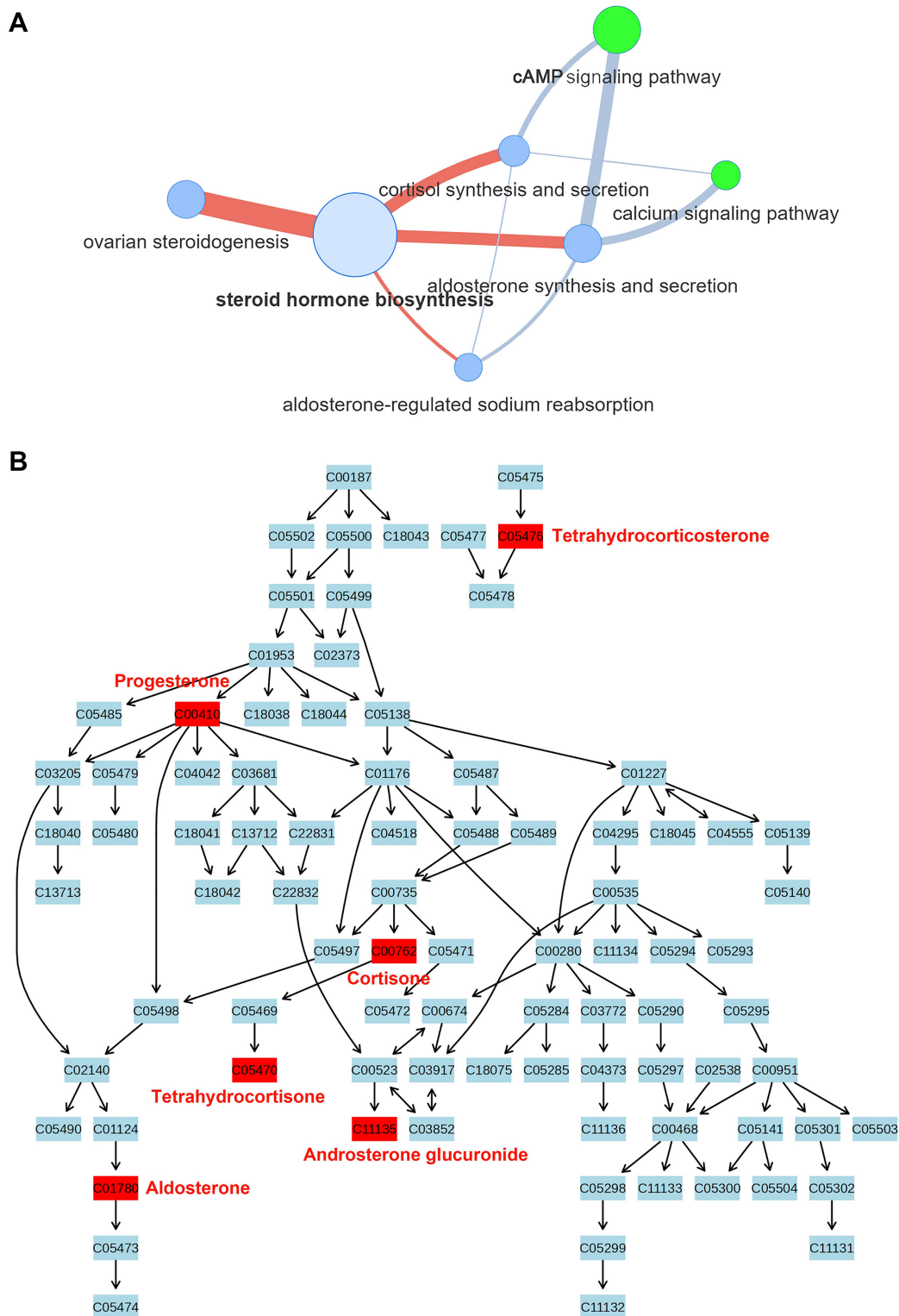


Fig. 4. Steroid hormone synthesis pathway is associated with IgAVN. (A) Pathway Interaction Network analysis shows interactions among steroid-related signaling pathways enriched in IgAVN patients, as identified by KEGG analysis. In the network, blue nodes represent pathways directly enriched by KEGG, while green nodes indicate pathways that closely interact with the enriched pathways but are not enriched in KEGG analysis. The size of each node corresponds to the number of compounds within that pathway, and the thickness of the edges reflects the number of shared compounds between pathways. (B) Six steroids (Red boxes) in steroid hormone biosynthesis pathway are significantly reduced in IgAVN patients compared to healthy controls, including tetrahydrocorticosterone, progesterone, cortisone, tetrahydrocortisone, androsterone glucuronide, and aldosterone.

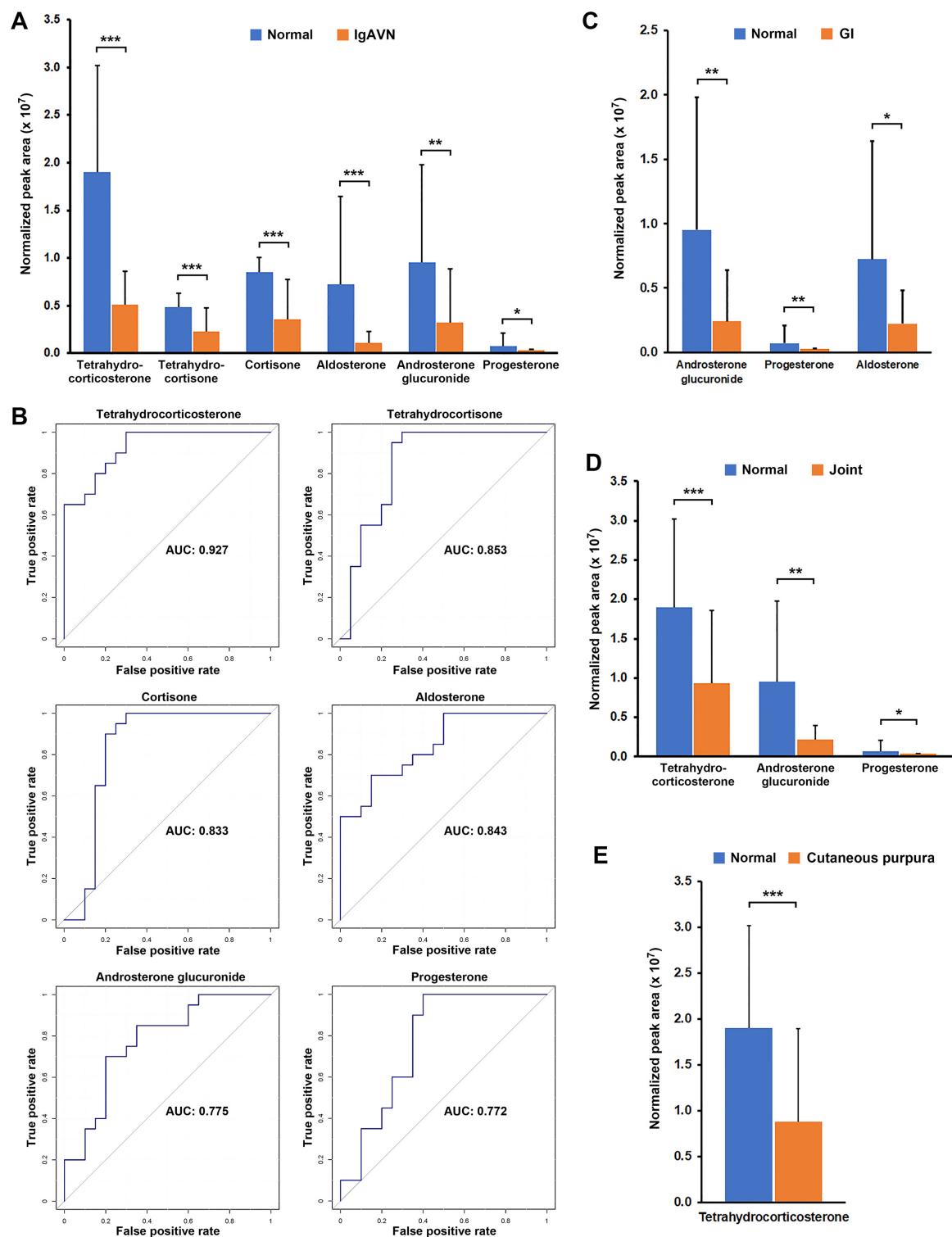


Fig. 5. Steroid metabolites are decreased in pediatric IgAV patients with various organ involvement. (A) Six steroid hormones are significantly reduced in IgAVN patients compared to healthy controls. (B) Receiver operating characteristic curves for differentially expressed steroids in IgAVN patients. AUC, area under the ROC curve. (C,D) Three steroids are significantly reduced in pediatric IgAV patients with GI and joint involvement, respectively, but one steroid differs between these two groups. (E) In comparison to healthy controls, significantly decreased tetrahydrocorticosterone is observed in IgAV patients with only cutaneous involvement. Data are presented as mean $\pm$ SD ($n = 20$ for all groups). AUC, area under the curve; ROC, receiver operating characteristic. $*p < 0.05$; $**p < 0.01$; and $***p < 0.001$.

Table 2. Age- and sex-adjusted fold change of steroids in patients compared with healthy controls.

Comparison/Steroid	Fold change	<i>p</i> value
<i>IgAVN vs Ctrl</i>		
Tetrahydrocorticosterone	0.28	1.34×10^{-6}
Tetrahydrocortisone	0.31	2.59×10^{-5}
Cortisone	0.12	2.64×10^{-5}
Aldosterone	0.18	0.0001
Androsterone glucuronide	0.12	3.76×10^{-6}
Progesterone [#]	0.76	0.0791
<i>GI vs Ctrl</i>		
Androsterone glucuronide	0.23	3.00×10^{-4}
Progesterone	0.58	4.00×10^{-4}
Aldosterone	0.38	0.0196
<i>Joint vs Ctrl</i>		
Tetrahydrocorticosterone	0.38	0.0055
Androsterone glucuronide [#]	0.46	0.0775
Progesterone [#]	0.74	0.1274
<i>Cutaneous vs Ctrl</i>		
Tetrahydrocorticosterone	0.31	3.00×10^{-4}

[#]Not significant.

IgAVN patients (Fig. 6A). In total, 33 proteins were significantly upregulated, while 154 proteins were downregulated in IgAVN patients (Fig. 6B). Notably, several proteins including coagulation factor V, complement factor H-related protein 1, and apolipoproteins C, D, and E, were significantly upregulated, while corticosteroid-binding globulin and complement protein C4B frameshift mutant were downregulated in IgAVN patients compared to healthy controls (Fig. 6B). KEGG analysis of these differentially expressed proteins demonstrated several key pathways associated with IgAVN pathogenesis, with the intestinal immune network for IgA ranking as the top pathway, alongside pathways for B cell receptor signaling, natural killer cell-mediated cytotoxicity, and infections by measles and Epstein-Barr virus (Fig. 6C). Notably, similar pathways were also enriched in the comparison between IgAV and IgAVN patients (**Supplementary Fig. 5**). Furthermore, protein-protein interaction analysis revealed a network of 37 differentially expressed proteins with strong interaction evidence (confidence score ≥ 0.5 , Fig. 6D). Gene ontology analysis indicated that the differentially expressed proteins in IgAVN patients were involved in coagulation regulation and cholesterol transport (Fig. 6E), both of which are closely associated with IgAVN pathology. Specifically, hypercoagulation represents a major clinical finding of IgAVN [22,23], while cholesterol transport is essential for generating steroid hormone precursors [24,25]. In addition, disease-gene association analysis indicated that the differentially expressed protein network was significantly linked to thrombophilia, blood coagulation disorders, glomerulonephritis, kidney disease, and purpura (Fig. 6F).

3.7 Correlation of Metabolomics and Proteomics

The association analysis further indicated that differentially expressed steroids, including aldosterone, cortisone, and tetrahydrocorticosterone were correlated with differentially expressed proteins in IgAVN patients compared to healthy controls (Fig. 7). Notably, these steroid hormones exhibited positive correlations with immunoglobulins while showing negative associations with coagulation factor V, endothelin-converting enzyme 1, keratin 4, and polymeric immunoglobulin receptor. These results suggest that decreased steroid hormones may influence immune response and coagulation, and thus linking to the pathological processes associated with IgAVN.

4. Discussion

IgA vasculitis (IgAV), an IgA-mediated systemic vasculitis, presents with a spectrum of clinical manifestations, ranging from cutaneous purpura to severe renal involvement [1,2]. IgAVN, in particular, carries a significant risk of long-term renal complications [6]. While previous studies have explored the individual contributions of metabolomics and proteomics in IgAV [10,11], we performed a comprehensive, integrated analysis of combined omics layers across varying disease severities, particularly focusing on the pathogenic mechanisms of IgAVN. Our study addresses a key knowledge gap in the combined metabolomic and proteomic landscape of IgAV and IgAVN and may contribute to our understanding of their pathogenesis.

Our metabolomic analysis revealed distinct metabolic profiles in IgAV and IgAVN patients compared to healthy controls, with steroid hormone biosynthesis emerging as

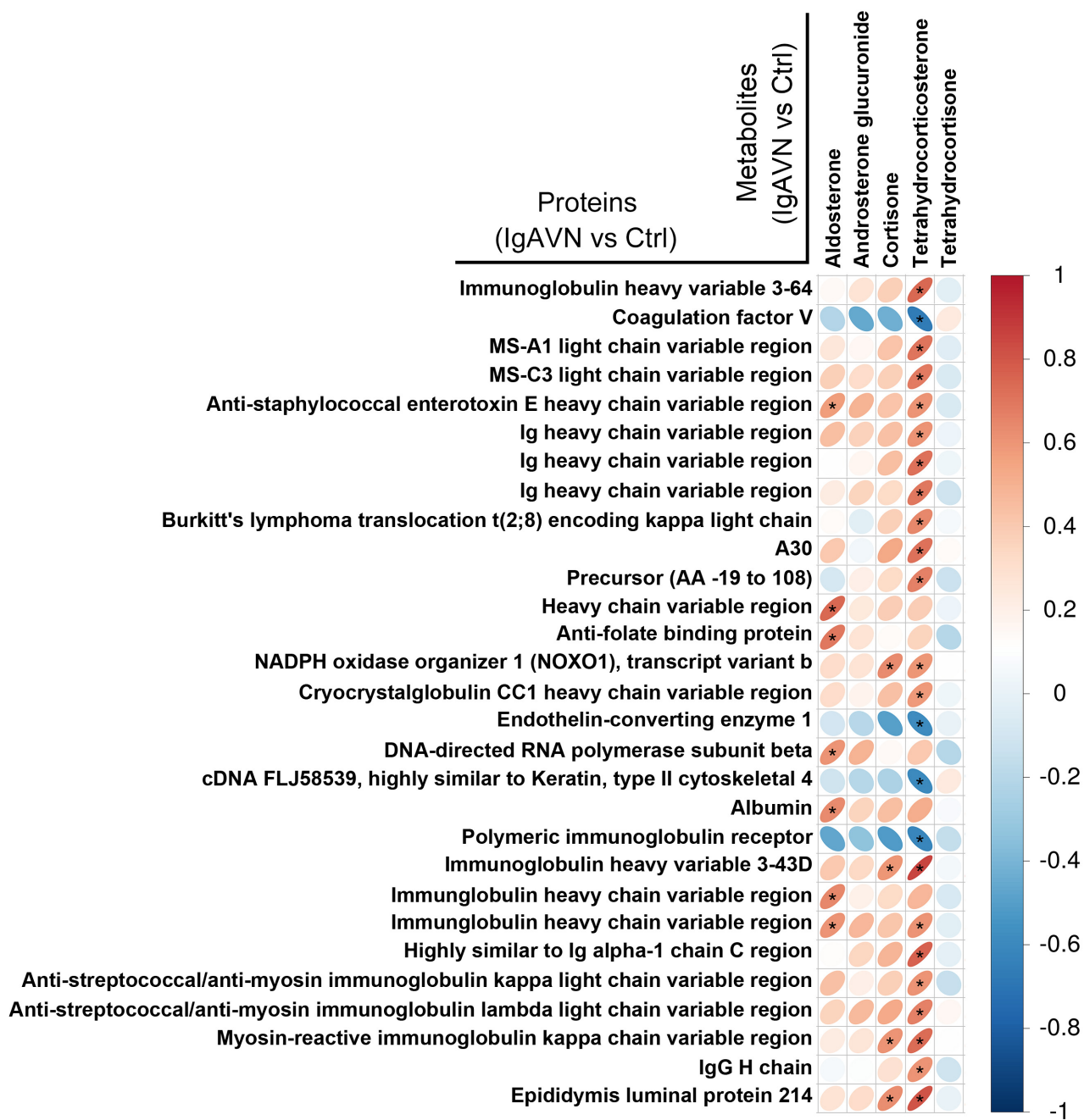


Fig. 7. Integrated analysis of metabolomic and proteomic data. Steroids identified by metabolomics are associated with proteins identified by proteomics. Of these, aldosterone, cortisone, and tetrahydrocorticosterone are significantly correlated with differentially expressed proteins in IgAVN patients. * $p < 0.05$.

a prominently altered pathway. This aligns with previous reports implicating metabolic dysregulation in IgAV, including alterations in amino acid metabolism and glycerophospholipid metabolism [26], but our results further demonstrate the specific importance of steroid hormone alterations and their correlation with disease severity. We observed that the number of differentially expressed metabolites increased with disease severity, with IgAVN exhibiting the most pronounced differences. This observation

suggests that select metabolites from plasma metabolomics could indicate phenotypic variation and disease severity, potentially complementing traditional clinical markers [15]. The unique metabolomic profile of IgAVN patients, characterized by a significant decrease in steroid hormones like tetrahydrocorticosterone, tetrahydrocortisone, cortisone, aldosterone, androsterone glucuronide, and progesterone, implicates that dysregulated steroid hormone biosynthesis may be linked to the development of IgAVN.

Nonetheless, whether the observed dysregulation of steroid hormone biosynthesis represents a causative factor or a consequence of IgAV/IgAVN remains unclear and requires longitudinal and functional studies.

Steroid hormones play crucial roles in immune regulation, inflammation, and vascular integrity, and their deficiency could contribute to systemic inflammation, IgA deposition, and vascular damage—characteristics of IgAV and IgAVN [27,28]. The gradual increase in the number of downregulated steroids corresponding to the severity of organ involvement from cutaneous purpura to joint, gastrointestinal tract, and ultimately kidney also supports the notion that decreased steroid production is intricately linked to the pathology of IgAV and IgAVN. This suggests a potential dose-dependent relationship between steroid hormone levels and disease severity, and offers rationale for the use of glucocorticoids in the treatment of the disease [29].

It is important to distinguish the systemic downregulation of endogenous adrenal steroidogenesis observed here from the therapeutic administration of exogenous synthetic glucocorticoids. Our data reveal a coordinated decline in multiple steroids, including tetrahydrocorticosterone, tetrahydrocortisone, cortisone, aldosterone, androsterone glucuronide, and progesterone, which reflects systemic dysregulation and impaired peripheral steroid metabolism rather than a simple cortisol deficiency amenable to replacement [30]. Exogenous synthetic glucocorticoids provide potent, supraphysiological anti-inflammatory signaling but are unable to replace the deficiency of other steroids, such as the mineralocorticoid aldosterone and progesterone, that constitute the physiological adrenal output [31]. Moreover, exogenous administration further suppresses residual hypothalamic-pituitary-adrenal (HPA) axis function through negative feedback, potentially exacerbating the endogenous deficiency [32]. Thus, while our findings support the rationale for corticosteroid intervention in IgAVN, they also underscore the need for regimens that better replicate the breadth of endogenous steroid physiology.

Our exploratory proteomic analysis revealed significant differences in protein expression between IgAV and IgAVN patients compared to healthy controls. Notably, one control sample clustered within the IgAVN group in the heatmap (Fig. 6A), although its expression pattern was more similar to other controls. This may reflect normal inter-individual biological variation, and such discrepancies may occasionally arise from the specific clustering algorithm or distance metric used in heatmap generation. Nevertheless, this isolated observation does not alter the overall interpretation of our results. Consistent with previous research [33,34], we observed an upregulation of proteins involved in platelet aggregation, complement activation, and the coagulation cascade in IgAV. These pathways are known to contribute to the inflammatory and thrombotic processes in vasculitis [35,36]. However, in IgAVN patients, we found a distinct proteomic signature char-

acterized by significant downregulation of corticosteroid-binding globulin and upregulation of apolipoproteins C, D, and E, alongside the enrichment of pathways related to the intestinal immune network for IgA. Downregulation of corticosteroid-binding globulin could further exacerbate deficiency of active steroid hormones [37]. Importantly, the intestinal IgA network has been implicated in the development of IgA nephropathy, sharing similarities with IgAVN [38]. These findings extend previous observations and provide novel insights into the specific pathogenic mechanisms underlying IgAVN. Taken together, our comprehensive approach provides a broader perspective on the complex interplay between metabolic and proteomic alterations in IgAV and IgAVN.

Elevated plasma IgA levels are common in patients with IgAV, and corticosteroid therapy leads to a significant reduction in these levels [39]. Similarly, glucocorticoids inhibit IgA production *in vitro* [40]. Conversely, decreased steroid hormones may impair the regulation of the immune system, leading to increased IgA production and deposition in the kidneys. The gut-kidney axis is increasingly recognized as an important factor in the pathogenesis of various kidney diseases [38,41]. Notably, our exploratory proteomic analysis demonstrated upregulated apolipoproteins C, D, and E in IgAVN patients. An increase in apolipoproteins could reflect a compensatory mechanism to transport lipids and cholesterol in the context of inflammation and vascular damage [42]. Additionally, apolipoproteins have been shown to modulate immune responses and interact with IgA [42,43]. Negative correlations between steroid hormones and coagulation factors, alongside positive correlations with immunoglobulins, further support a model in which decreased steroid could disrupt the balance between coagulation and immune responses, contributing to the thrombotic and inflammatory milieu in IgAVN. Furthermore, endothelin-converting enzyme 1 (ECE1), which correlates negatively with steroid hormones in our study, is involved in the production of endothelin-1, a potent vasoconstrictor that is positively correlated with IgAV [44,45]. Based on these findings, we propose a mechanistic model linking alteration in steroid biosynthesis, apolipoprotein production, and intestinal IgA network dysfunction to IgAVN pathogenesis. This could infer development of novel therapeutic targets, including selective steroid hormone receptor modulators or apolipoprotein-based therapies [46].

Limitations

The advantages of this study include the use of a well-defined patient cohort with varying clinical manifestations, the integration of metabolomic and proteomic data, and the identification of novel pathways and metabolites associated with IgAVN. Nevertheless, we acknowledge the limitations of cross-sectional study design in establishing relationships between the identified metabolites and pro-

teins and disease progression. Longitudinal and quantitative studies are needed to observe changes in specific metabolites over time and assess their predictive value. Additionally, the sample size, particularly for proteomics, while adequate for detecting statistical significance, could be further increased in future studies to enhance power and validate our findings across diverse populations. Furthermore, potential confounding factors, such as dietary habits, were not fully controlled for in this study and could influence the results [47]. Pubertal status, as another potential confounding factor, was not directly assessed; instead, age and sex were included as covariates in the ANCOVA to account for development-related variation in steroid levels. Moreover, independent validation of differentially expressed steroids in additional cohorts is currently lacking; such efforts would further establish the clinical significance of these metabolites. This is an ongoing project being investigated by our group. Finally, functional studies using *in vitro* and *in vivo* models are warranted to further investigate the effects of dysregulated steroid hormone biosynthesis on the development of IgAVN.

5. Conclusions

In summary, this cross-sectional discovery study provides a comprehensive metabolomic and proteomic characterization of IgAV and IgAVN patients, revealing distinct molecular signatures associated with disease severity and clinical manifestations. Our findings highlight that steroid biosynthesis dysregulation, apolipoprotein alterations, and the intestinal IgA network are strongly associated with IgAVN. These results characterize molecular associations in IgAVN and provide a foundation for future mechanistic and diagnostic inquiry.

Availability of Data and Materials

All data are included in this published article and **Supplementary files**. Further inquiries can be directed to the corresponding authors.

Author Contributions

XW, data analysis and visualization, figure preparation, funding acquisition, writing the manuscript, and critical review of the manuscript; RM, LM, KS, and DW, participant recruitment, sample collection and preparation, data acquisition and analysis; reviewing and revising the manuscript. YY, conception and study design, participant recruitment, data acquisition, data analysis and interpretation, supervising the study, funding acquisition, figure preparation, and writing and reviewing the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Lanzhou University Second Hospital (Approval number: 2017A-100) and the Ethics Committee of Nantong Maternity and Child Healthcare Hospital (Approval number: Y2022013). Written informed consent to participate in this study was provided by the participants' parents or legal guardians. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Acknowledgment

The authors gratefully thank the participants and their family for facilitating this work.

Funding

This study was supported by the Jiangsu Health Innovation Team Program Seed Grant (CX2023002, to Y.Y.), the Lanzhou University Second Hospital Cuiying Science and Technology Innovation Project (CY2017-MS16, to Y.Y.), the Jiangsu Distinguished Medical Expert Program (2019, to X.W.), and the Jiangsu Health Innovation Team Program (2020, to X.W.).

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/FBL54013>.

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