Review Article

Recent progress in metabolomic analysis of acute coronary syndrome: a narrative review

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Background and Objective: Acute coronary syndrome (ACS) is a common cardiovascular disease in clinical practice. It is caused mainly by vulnerable plaque rupture (PR) or surface plaque erosion (PE) caused by serious thrombotic events, and eventually leads to myocardial blood supply insufficiency or necrosis. The disease has high morbidity and mortality rates. In this study, we review the literature on biomarkers of ACS metabolites and modification of disease by altering related metabolic pathways through drugs, aiming to provide clarity on potential biomarkers of disease identified to date.

Methods: PubMed was used for literature review. From January 1, 2014 to December 3, 2024, English articles on clinical trials, randomized controlled trials of metabolomics studies in ACS were included.

Key Content and Findings: In this review, we discuss the advantages and disadvantages of three techniques currently used for metabolomic analysis. In addition, the recent decade of metabolomic approaches to the discovery of potential diagnostic and prognostic biomarkers for ACS is reviewed. It was found that the metabolites changed in patients with ACS were mostly amino acids, lipids and carbohydrates. Tryptophan and glutamine can be used as potential diagnostic biomarkers. Mannitol and ceramide can be used as prognostic biomarkers. Drugs can improve disease by affecting changes in metabolites in the body.

Conclusions: ACS studies based on metabolomics have demonstrated great potential for identifying disease-related metabolomic features in the discovery of potential biomarkers for diagnosis and prognosis and mechanisms of drug therapy.

Keywords: Diagnostic biomarker; prognostic biomarkers; metabolomic; acute coronary syndrome (ACS)

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Introduction

Acute coronary syndrome (ACS) is a clinical syndrome caused by acute myocardial ischemia, and is one of the leading causes of death worldwide (1). The main pathogenesis of ACS is the sudden rupture and superficial erosion of atherosclerotic plaque in the process of occurrence and development, which causes thrombosis and eventually leads to insufficient blood supply or necrosis of myocardium (2-4). ACS subtypes include unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) (5). Currently, the diagnosis of ACS requires a combination of clinical and electrocardiographic (ECG) signals, and myocardial injury markers are necessary to distinguish the various subtypes of ACS. However, not only may biomarkers such as troponin be increased in other diseases, but the identification of different subtypes also requires ongoing detection of ECG and biomarkers of myocardial damage in conjunction with clinical

Table 1 The search strategy summary

Items	Specification
Date of search	03/15/2022–27/08/2024
Database searched	PubMed
Search terms used	("acute coronary syndrome" OR "unstable angina" OR "NSTEMI" OR "STEMI") AND "metabolomics"
Timeframe	01/01/2014–12/03/2024
Inclusion and exclusion criteria	Inclusion: primary investigational, clinical trial
	Exclusion: Review etc.
Selection process	Articles were selected and reviewed by J.L. and T.L.
Any additional considerations, if applicable	Additional relevant references were included during the primary literature search

NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

manifestations (6). There is undoubtedly an urgent need for more low-cost but highly sensitive and specific biomarkers.

With the continuous advancement of science and technology in the field of systems biology, after genomics and proteomics, metabolomics has also entered everyone's field of vision (7). Metabolomics can qualitatively and quantitatively analyze all small molecule metabolites in an organism, providing an avenue for studying the relative relationships between physiological and pathological changes. Since dynamic perturbations of the genome, transcriptome, and proteome can all be reflected by changes in an organism's metabolites, metabolites can efficiently link genotype to phenotype (8). For this reason, metabolomics can provide information about organisms under normal or pathological conditions, and reflect changes in organisms in response to metabolites stimulated by external stimuli (9). Metabolomics has been widely used to discover novel diagnostic and prognostic biomarkers and more therapeutic targets to improve disease outcomes (10).

In previous studies, researchers have also reviewed the metabolomic-related studies of ACS. In 2019, Pouralijan Amiri *et al.* (10) provided a comprehensive review of the pathogenesis of ACS, metabolomics techniques, and several studies on the application of metabolomics for detecting ACS. Their work highlights that metabolomics is a robust method for characterizing metabolic disturbances associated with various cardiovascular diseases. In 2021 and 2023, researchers augmented the existing technical methodologies in metabolomics, elucidated the experimental protocols for detecting diseases through metabolomics, and synthesized findings from previously identified altered metabolic pathways associated with ACS (1,11). This paper focuses more on the potential diagnostic and prognostic biomarkers and their diagnostic and prognostic abilities found in previous studies based on metabolomics, and summarizes the types they belong to, so as to find the metabolic pathways that are most prone to change when diseases occur. We present this article in accordance with the Narrative Review reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-431/rc).

Methods

This study is a narrative review aimed at identifying and searching current literature on studies related to the metabolomics of ACS. A combination of "acute coronary syndrome", "unstable angina", "NSTEMI, STEMI" and "metabolomics" was used to search PubMed literature in English from January 2014 to December 2024. We included articles that identified potential diagnostic and prognostic markers for ACS and their subtypes, as well as articles that identified mechanisms of drug treatment for the disease through metabolomics. The main objective of our review was to summarize the potential diagnostic and prognostic markers identified by metabolomics over the last decade and to explore the changes in metabolic pathways that most commonly occur in ACS. *Table 1* summarizes the search strategies used in our review, the full electronic search strategy can be seen in Table S1.

Techniques applied to metabolomics analysis

Currently, nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry are the two most common

Table 2 A summary of the important advantages and disadvantages of NMR and MS techniques

Technique	Advantages	Disadvantages
NMR	• Simple sample pre-processing	• Low sensitivity
	• High stability and reproducibility	• Resonance has multiplicity, noise will repeat with the signal, low resolution
	• Non-destructive to samples	
	• Detects liquids as well as solids, gases, and tissue samples	
	• Simulates physiological conditions detection	
	• Provides accurate information on the molecular structure and concentration about compounds	
GC-MS	• Ultra-high column efficiency and peak capacity, better separation efficiency	• Complex sample preparation
	• Available for analysis of volatile and non-polar metabolites	• No thermally unstable substances detection
	• Database available for identification provides relatively qualitative results	• No polar metabolites detection
LC-MS	• Smaller sample size required	• Low reproducibility
	• Proven data processing platform available	• Ion suppression
	• Suitable for analysis of substances with highly repetitive structures	• No gas mixture detection
	• Not limited by difficult volatility and thermal instability	

GC-MS, gas chromatography mass spectrometry; LC-MS, liquid chromatography mass spectrometry; NMR, nuclear magnetic resonance.

analytical tools used in metabolomics studies (12). NMR is a pioneering platform for metabolomics that combines non-destructiveness, unbiasedness, high stability and reproducibility. Its main advantages are the small sample size required and simple pre-treatment, which can provide accurate molecular structures of compounds (13). However, the greatest problem is that it is not as sensitive as mass spectrometry and is prone to signal overlap, leading to inaccurate results (14). Mass spectrometry is generally combined with gas chromatography (GC-MS) and liquid chromatography (LC-MS), the overall sensitivity of mass spectrometry is higher than that of NMR, and the application of LC-MS is more widespread (15). LC-MS detection of metabolites is not limited by difficult volatility and thermal instability, and sample preparation is simpler than GC-MS as no derivatization is needed (8). GC-MS can be used for the detection of volatile or non-polar metabolites but sample preparation is complex. And it is very difficult to detect non-volatile or thermally unstable, easily degradable substances (12). The main advantages and disadvantages of NMR, LC-MS and GC-MS techniques are summarized in *Table 2*. In general, it is difficult to detect all metabolites with a single detection technique alone, so an increasing number of groups are now combining NMR and MS, using their complementary functions to improve the quality of detection, and to identify more metabolic compounds (16).

Application of metabolomics to discover potential biomarkers of ACS

The development of disease is often associated with genetic or phenotypic changes in the organism, so we have been able to diagnose and predict the occurrence of disease through changes in genes, proteins and metabolites. In contrast, most researchers believe that metabolites are better suited for clinical biomarker development and research (17). The number of biomarkers has been increasing in recent years, and over the past decade, many researchers have conducted extensive research on diagnostic and prognostic biomarkers associated with ACS. A comprehensive list of metabolomics studies on ACS focusing on diagnostic biomarkers and prognostic biomarkers is presented in *Tables 3*,*4*.

Metabolomics-based diagnostic biomarker analysis of ACS

Currently, the diagnosis of ACS relies on comprehensive analysis of clinical manifestations, electrocardiograms, and myocardial biomarkers of myocardial injury (74).

Table 3 A list of metabolomic studies focusing on diagnostic biomarkers of ACS

No.	First author, year	Disease	Sample size	Source	Technique	Biomarker
1	Yin *et al.* (18), 2017	ACS	20 ACS; 20 non-ACS	Plasma	LC-MS	7 LysoPCs, 2 LysoPEs, 2 glycerophosphocholines, 3 Sphingomyelin, L-tryptophan, glucose, caffeine, paraxanthine, palmitoleic acid, indoleacrylic acid, oleic acid
2	Zhong *et al.* (19), 2021	ACS	284 ACS; 130 HCs	Plasma	LC-MS	Lysophosphatidylcholine (20:4), lysophosphatidylcholine ((16:0), 5-oxo-D-proline, creatinine
3	Song *et al.* (20), 2021	ACS	45ACS; 29 HCs	Serum	UPLC-MS	lysoPC(20:4(8Z,11Z,14Z,17Z)/0:0), sphingomyelin (d18:0/16:0), Sphingomyelin (d18:1/14:0)
4	Wei *et al.* (21), 2021	ACS	21 ACS anxiety; 26 ACS	Plasma	LC-MS	Serotonin; oleoylcarnitine; aminoethoxyacetic acid; tryptophan, argininosuccinic acid; homoserine,17-hydroxypregnenolone sulfate; 19-hydroxyandrost-4-ene-3,17-dione; 3-alpha-androstanediol glucuronide; 5a-tetrahydrocorticosterone; androsterone sulfate; LysoPC(15:0); LysoPC(16:0); LysoPC(18:1(11Z)); LysoPC(20:5(5Z,8Z,11Z,14Z,17Z)); Lyso PC(22:5(4Z,7Z,10Z,13Z,16Z)); LysoPC(22:6(4Z,7Z,10Z,13Z, 16Z,19Z)); 4-hydroxynonenal; thromboxane B2; triglyceride; 4-hydroxycyclohexylcarboxylic acid; Trans-aconitic acid; 7-methylguanine; 11-Oxo-androsterone glucuronide; deoxycholic acid 3-glucuronide; 5-androstenetriol; tetrahydrocortisone; 25-Hydroxyvitamin D2; alpha-carboxyethyl; hydroxychroman; trigonelline; 3-carbamoyl-2-phenylpropionaldehyde; phosphorylcholine; isobutyryl-L-carnitine; glycerophosphocholine; LysoPC(18:0); hippuric acid; alanine
5	Fu *et al.* (22), 2023	ACS	44 UA; 77 AMI; 29 HCs	Serum	LC-MS/MS	Octanoylcarnitine; cyclic GMP; LysoPC(18:2(9Z,12Z)); 2-ketobutyric acid; indoxyl sulfate
6	Qiu *et al.* (23), 2023	ACS	500 ACS; 500 HCs	Serum	LC-MS/MS	1,5-anhydro-D-glucitol; tetracosanoic acid; aspartylphenylalanine
7	Shibata *et al.* (24), 2024	ACS	18 ACS; 24 HCs	Serum	UPLC-Q-TOF/MS	Isocitrate; lysine; tryptophan
8	Fan *et al.* (25), 2016	AMI	2,019 center 1; 71 center 2; 68 center 3; 166 center 4	Plasma	LC-Q-TOF/MS	LysoPC 16:1; glycodeoxycholic acid LysoPC 18:2; LysoPC 16:0; palmitoylethanolamide; choline 5-hydroxy; tryptamine; threonine; acetylcarnitine; LysoPC 14:0; tryptophan; 2α-methyl-5α-androstane-3, 17-dione; trimethylamine 3-Octanone; decenyl acetate; fumaric acid; MG 18:0/0:0/0:0; phosphatidylcholine; CerP d18:0/16:0; N-methylisoleucine; LysoPE 22:6; Undecan-3-ol; ethylchenodeoxycholic acid; LysoPE 20:4; LysoPE 22:5; succinic acid; Valine; LysoPC 20:3; Indole-3-ethanol; LysoPC 24:0; LysoPC 22:5; LysoPC 22:6; LysoPE 16:0; LysoPE 18:0; LysoPE 20:1; 3-methyl-2-butene-1-thiol; PE 12:0/22:6; LysoPC 20:5; PG 13:0/14:0; LysoPE 18:3; PG 15:0/14:0; glycerophosphocholine; LysoPE 22:1 PE 20:0/0:0 PE 18:0/0:0 PI 18:2/0:0 2-Nonynoic acid; LysoPC 20:4; PE 21:0/0:0; octadecadienoic acid; CerP d18:1/8:0; LysoPC 10:0; LysoPC 18:0 LysoPE 18:1; PI 18:3/0:0; 2-octenoylcarnitine; phosphocholine; docosahexaenoic acid; LysoPC 18:1; glycocholic acid; γ-aminobutyric acid
9	Aa *et al.* (26), 2021	AMI	230 chest pain patients (85 MI; 61 non-MI); 84 HC	Plasma	LC-MS; GC-MS	Methionine; L-phenylalanine; deoxyuridine

Table 3 (*continued*)

Table 3 (*continued*)

No.	First author, year	Disease	Sample size	Source	Technique	Biomarker
10	Martin-Lorenzo *et al.* (27), 2015	AMI	7 experimental group rabbits; 7 control group rabbits	Urinary	1H-NMR; LC-MS/MS	Kynurenine; N-acetyl neuraminic acid; scyllo-inositol
11	Xu *et al.* (28), 2016	AMI	38 SA; 34 AMI; 71 HCs	Serum	UPLC-Q-TOF/MS	Ceramide (d18:0/12:0); ceramide (t18:0/16:0); dehydroepiandrosterone sulfate
12	Jiang *et al.* (29), 2020	AMI	33 SPs; 32 VPs	Serum	LC-MS	Betaine; 1-heptadecanoyl-sn-glycero-3-phosphocholine; methylmalonate; hippurate; cis-aconitate; paraxanthine; acetylcarnitine; undecylic acid; pyruvate
13	Guo *et al.* (30), 2021	AMI	21 young AMI; 15 older AMI; 9 young HCs	Plasma	UPLC-MS/MS	Arachidonic acid; alpha-linolenic acid; 8,11,14-eicosatrienoic; adrenic acid; gamma-linolenic acid; linoleic acid
14	Petras *et al.* (31), 2020	AMI	30 AMI; 30 HCs	Plasma	1H-NMR	3-hydroxybutyrate; glutamine; alanine; inosine; myo-inositol; glycerol; pyruvate; tryptophan
15	Li *et al.* (32), 2020	AMI	136 NOCAD; 118 AMI	Serum	UPLC-Q-TOF/MS	5-hydroxydantrolene; acetylglycine; glycerophospholipid; fatty acid; glutarylglycine; threoninyl-glycine; acylcarnitines
16	Deng *et al.* (33), 2018	AMI	45 AMI; 45 CPC	Serum	1H-NMR	Phosphorylcholine; histidine; glycerophosphorylcholine; unsaturated fatty acids; citrate; gamma-glutamylthreonine; hypoxanthine; α-glucose; choline; isoleucine; valine; lysine; leucine; glutamate; tyrosine; lactate; alanine; phenylalanine; glutamine
17	Wang *et al.* (34), 2017	AMI	CAL-rats, 34 infarcted myocardia; 34 non-infarcted myocardia	Tissue	GC-MS	Histidine; lactate; glutamate
18	Zhang *et al.* (35), 2018	AMI	2,019 center 1; 71 center 2; 68 center 3; 166 center 4	Plasma	LC-Q-TOF/MS	N-acetylneuraminic acid
19	Park *et al.* (36), 2015	AMI	70 angina; 70 MI; 70 HCs	Serum	UPLC-Q-TOF/MS	Ceramide; palmitic acid; diacylglycerol; plasmalogen; sphingomyelin
20	DeFilippis *et al.* (37), 2017	AMI	11 thrombotic MI; 12 non-thrombotic MI	Plasma	UPLC-MS/MS GC-MS	Corticosterone; 1-palmitoylglycerol; 2-linoleoylglycerol; 2-oleoylglycerol; 2-palmitoylglycerol; 1-linoleoylglycerol; androsterone glucuronide; cortolone-3-glucuronide; dihydrocortisol; pregnenolone sulfate; tetrahydroaldosterone-3-glucuronide; 1-arachidonylglycerol; glutamine
21	Zhu *et al.* (38), 2018	AMI	30 MI; 30 HCs	Plasma	UPLC-Q-TOF/MS	Phosphatidylserine; lysoPC(16:0); lysoPC(18:2); lyso-PC (C18:1); C16-sphingosine; N-methyl arachidonic amide; linoleamidoglycerophosphate choline; N-(2-methoxyethyl) arachidonic amide; arachidonic acid; linoleic acid
22	Lu *et al.* (39), 2017	AMI	10 HCs; 10 SA; 8 MI	Plasma	UHPLC-Q-TOF/MS	Isoprostanes; oxidized phospholipid; oxidized PL; glycerophospholipid; arachidonic acid; linoleic acid
23	Lee *et al.* (40), 2015	AMI	68 MI; 68 HCs	Serum	UPLC-Q-TOF/MS	Proline; arginine; uridine; 2-hydroxyisobutyric acid; 9-decenoylcarnitine; decanoylcarnitine; suberic acid; malic acid; 3-indolepropionic acid; citric acid; azelaic acid; phenylalanyl-phenylalanine; phenylalanyltryptophan; glycocholic acid; cholic acid; L-acetylcarnitine; 2-hydroxy-3-metylbutyric acid; betaine; choline; Inosine; uric acid; hypoxanthine; isoleucine; creatine; phenylalanine

Table 3 (*continued*)

Table 3 (*continued*)

No.	First author, year	Disease	Sample size	Source	Technique	Biomarker
24	Holmes *et al.* (41), 2018	AMI	912 MI; 1,146 IS; 1,138 ICH; 1,466 HCs	Plasma	NMR	Trimethylamine; carnosine; glycoprotein acetyls; indol-3-acetate; β-hydroxybutyrate; creatine; docosahexaenoic acid; leucine; histidine; isoleucine; glutamine
25	Ward-Caviness *et al.* (42), 2017	AMI	2,257 AMI	Serum	LC-MS	Lysophosphatidylcholine 17:0; lysophosphatidylcholine 18:2; arginine
26	McKirnan *et al.* (43), 2019	AMI	10 surgical groups; 6 sham groups	Serum, tissue	GC-TOF/MS	Phosphoethanolamine; Beta-alanine; aminomalonate; stearic acid; 2-hydroxyvaleric acid; palmitoleic; benzoic Acid; succinic acid; threonic acid; glutathione; ethanolamine; cholesterol; dehydroascorbic acid; nicotinamide; taurine; conduritol-beta-epoxide; hydroxycarbamate; isothreitol; methylphosphate; sulfuric acid (Sulfate); phosphate; methionine; alpha-linolenic acid; malic acid; hypoxanthine; urea; phenylalanine; alanine
27	Khan *et al.* (44), 2020	AMI	112 AMI; 89 non-risk controls	Serum	HR-MS	Cysteic acid; L-cysteine; t-methylhistidine; L-homocysteine; sulfinic acid; L-cysteine; sulfinic acid; tryptophan
28	Huang *et al.* (45), 2023	AMI	103 AMI; 84 STEMI; 19 NSTEMI	Plasma	LC-MS/MS	Betaine; trimethylamine N-oxide
29	Lim *et al.* (46), 2022	AMI	101 AMI; 66 HCs	Plasma	LC-MS/MS	Glycerophospholipid
30	Xia *et al.* (47), 2023	AMI	59 diabetes AMI; 59 non-diabetes-AMI	Plasma	LC-MS/MS	N-lactoyl-phenylalanine; lysophosphatidylcholines
31	Naz *et al.* (48), 2015	STEMI	16 STEMI; 16 NSTEMI 20 STEMI; 26 NSTEMI	Serum	CE-MS; HILIC-MS	C02-carnitine
32	Huang *et al.* (49), 2018	STEMI	44 STEMI (22 LMCAD; 22 non-LMCAD); 22 HCs	Plasma	UPLC-MS/MS	Dehydrophytosphingosine; 9-cis-retinoic acid; 1H-Indole-3-carboxaldehyde; lysophosphatidylcholines
33	Gundogdu *et al.* (50), 2020	STEMI	20 STEMI; 15 HCs	Serum	LC-Q-TOF/MS	L-proline; glycerol; lysoPC (18:2(9Z)); propionic acid; butyric acid; succinate; fumaric acid; L-lactic acid; caffeine; phosphatidylethanolamine; glycine; palmitic acid; oleic acid; citrate; taurine; urea; alanine; leucine; isoleucine
34	Goulart *et al.* (51), 2019	STEMI	15 STEMI; 15 HCs	Plasma	UPLC-MS/MS and FIA-MS	Phosphatidylcholines; sphingomyelin; lysophosphatidylcholines
35	Luo *et al.* (52), 2022	STEMI	42 STEMI patients (21 consecutive VF and 21 non-VF)	Plasma	UPLC-MS/MS	Dehydrophytosphingosine; 9-cis-retinoic acid
36	Ali *et al.* (53), 2016	STEMI	30 STEMI;15 UA; 15 HCs	Serum	GC-MS; SPME-GC/MS; 1H-NMR	Pyruvate; lactic acid; maleic acid; uric acid; urea; H2S.; β-hydroxybutyric acid; choline; betaine; citrulline; glycerol
37	Chorell *et al.* (54), 2020	STEMI	50 STEMI; 50 NSTEMI; 100 controls	Serum	GC-TOF/MS; LC-TOF/MS	Aspartate; branched-chain amino acids; sphingosine 1-phosphate; lysophospholipids; C02-carnitine; C5iso-carnitine; acylcarnitines; valine; isoleucine
38	Luo *et al.* (55), 2023	STEMI	STEMI (36 PR; 36 PE)	Plasma	LC-MS	Salicylic acid; proline; docosahexaenoic acid
39	Laborde *et al.* (56), 2014	NSTEMI	35 NSTEACS; 35 HCs	Plasma	GC-MS	5-OH-tryptophan; 2-OH-butyric acid; 3-OH-butyric acid

Table 3 (*continued*)

Table 3 (*continued*)

No.	First author, year	Disease	Sample size	Source	Technique	Biomarker
40	Ameta *et al.* (57), 2016	UA	65 UA; 62 HCs	Serum	1H NMR	Glutamine; alanine; inosine; adenine; valine
41	Wang *et al.* (58), 2019	UA	39 UA; 40 HCs	Plasma	UPLC-Q-TOF/MS	Lysophosphatidylcholines; LysoPE
42	Yao *et al.* (59), 2017	UA	101 UA;132 HCs	Serum	1H-NMR	Trimethylamine N-oxide; phosphocholine; isoleucine; valine; lysine; leucine; creatine; glutamate; threonine; 1-methylhistidine; myo-inositol; lactate; high-density lipoprotein; low density lipoprotein; very low-density lipoprotein; total cholesterol; choline; phenylalanine; glycerophosphocholine; 3-hydroxybutyrate; glutamine
43	Li *et al.* (60), 2015	UA	27 UA; 20 HCs	Urinary	1H-NMR	Choline; phenylalanine; citrulline; L-alanine; N-methylnicotinamide; tryptophan; 3-hydroxybutyrate; creatinine; glutamine; lysine
44	PouralijanAmiri *et al.* (61), 2020	UA	94 UA; 32 HCs	Plasma	1H-NMR	17-hydroxyprogesterone; 2-hydroxyestrone; 2-methoxyestradiol; androstenedione; deoxycorticosterone; etiocholanolone; 2-methoxyestrone; 2-hydroxyestradiol; estradiol
45	Sun *et al.* (62), 2013	UA	45 UA; 43 AS	Plasma	RRLC-Q-TOF/MS	Glutamic acid; deoxyribose 1-phosphate; PG(16:0/16:0); PG(20:5(5Z,8Z,11Z,14Z,17Z)/20:1(11Z)); decenedioic acid; MG(0:0/18:2(9Z,12Z)/0:0); MG(0:0/18:3(9Z,12Z,15Z)/0:0); MG (20:5(5Z,8Z,11Z,14Z,17Z)/0:0/0:0); 7,8-dihydropteroic acid; indoxylsulfuric acid; Histidinyl-valine; 18-hydroxycorticosterone; 3b,16a-dihydroxyandrostenone sulfate; choline; phytosphingosine; lactate
46	Liu *et al.* (63), 2022	UA	10 UA;10 HCs	Serum	LC-MS	p-Cresol; sulfate; ceramide
47	Hao *et al.* (64), 2024	UA	33 UA; 38 MI; 24 HCs	Serum	UPLC-Q-TOF/MS	2-hydroxyhexanoic acid; medronic acid; butylbenzene sulfonamide; phosphocholine

ACS, acute coronary syndrome; AMI, acute myocardial infarction; AS, atherosclerosis; CAL, coronary artery ligation; CE-MS, capillary electrophoresis-mass spectrometry; CerP, ceramide phosphate; CPC, chest pain controls; FIA-MS, flow injection analysis-mass spectrometry; GC-MS, gas chromatography mass spectrometry; GC-TOF/MS, gas chromatography-time-of-flight mass spectrometry; HC, health control; HILIC-MS, hydrophilic interaction chromatography-mass spectrometry; HR-MS, high-resolution mass spectrometry; ICH, intracerebral hemorrhage; IS, ischemic stroke; LC-MS, liquid chromatography mass spectrometry; LC-MS/MS, liquid chromatography tandem mass spectrometry; LC-Q-TOF/MS, liquid chromatography-quadrupole time-of-flight mass spectrometry; LMCAD, left main coronary artery disease; lysoPC, lysophosphatidylcholine; lysoPE, lysophosphatidylethanolamine; MG, monoglyceride; MI, myocardial infarction; NMR, nuclear magnetic resonance; NOCAD, non-obstructive coronary artery disease; NSTEACS, Non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PE, plaque erosion; PG, phosphatidylglycerol; PI, phosphatidylinositol; PL, phospholipid; PR, plaque rupture; RRLC-Q-TOF/MS, rapid resolution liquid chromatography-quadrupole time-of-flight mass spectrometry; SA, stable angina; SP, stable plaque; SPME-GC/MS, solid phase microextraction-gas chromatography/mass spectrometry; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; UHPLC-Q-TOF/MS, ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry; UPLC-MS, ultra-performance liquid chromatography mass spectrometry; UPLC-MS/MS, ultra-performance liquid chromatography tandem mass spectrometry; UPLC-Q-TOF/MS, ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry; VF, ventricular fibrillation; VP, vulnerable plaques.

Although the continuous advancement of technology has greatly improved the accuracy of diagnosis, there are still insufficient and certain limitations. Although markers of myocardial injury have good sensitivity, the specificity of creatine kinase-MB (CK-MB) is not strong, and an increase in troponin reflects only myocardial injury (75). If there is no clinical evidence that the injury is related to coronary ischemia, the myocardial injury may be caused by other causes (76). Metabolomics studies can detect a large number of metabolites, and metabolites can also be effective new

Table 4 A list of metabolomic studies focusing on prognostic biomarkers of ACS

No.	First author, year	Disease	Sample size	Source	Technique	Biomarker
1	Vignoli *et al.* (65), 2019	AMI	AMI 832 survivors; 146 deceased	Serum	1H NMR	Valine; 3-hydroxybutyrate; formate; mannose; creatinine; histidine; proline; acetone
2	Liu *et al.* (66), 2022	AMI	445 HCs; 347 AMI; 79 AMICVD	Serum	1H NMR	Glutamine; creatine; threonine; N-acetylphosphinothricin; inosine; myo-inositol; histidine; acetone; alanine; trimethylamine N-oxide
3	Vignoli *et al.* (67), 2020	AMI	AMI: 702 survivors; 123 deceased	Serum	1H NMR	Mannose; creatinine
4	Surendran *et al.* (68), 2019	STEMI	108 plasma samples from 27 STEMI patients	Plasma	LC-Q-TOF-MS	Linoleoyl carnitine; 1-linoleoylglycerophosphocholine; pentadecanoic acid
5	Liu *et al.* (69), 2021	STEMI	48 survivors; 48 non-survivors	Plasma	UPLC-MS	N-acetyl-leukotriene E4; 3-methyl-2-butene-1-thiol; 4-hydroxy-6-docosanone
6	Laaksonen *et al.* (70), 2016	ACS	Corogene; SPUM-ACS; BECAC	Plasma	Cohort analysis	Ceramide
7	Kraler *et al.* (71), 2023	ACS	2,619 ACS	Plasma	Cohort analysis	LDL electronegativity
8	Lozhkina *et al.* (72), 2024	ACS	73 ACS; favorable outcome; fatal outcome	Plasma	HPLC-MS/MS	Phosphoribosyl pyrophosphate; 3-hydroxycapric acid; beta-alanine
9	Usova *et al.* (73), 2024	ACS	110 ACS	Plasma	UPLC-MS	Ceramide

ACS, acute coronary syndrome; AMI, acute myocardial infarction; AMICVD, acute myocardial infarction-cardiovascular disease; BECAC, Bergen Coronary Angiography Cohort; HC, health control; HPLC-MS/MS, high performance liquid chromatography-tandem mass spectrometry; LC-Q-TOF-MS, liquid chromatography-quadrupole time-of-flight mass spectrometry; NMR, nuclear magnetic resonance; SPUM-ACS, Special Program University Medicine-Inflammation in Acute Coronary Syndromes; STEMI, ST-segment elevation myocardial infarction; UPLC-MS, ultra-performance liquid chromatography tandem mass spectrometry.

biomarkers.

For ACS, there have been a number of articles in which valuable diagnostic biomarkers have been identified. In 2017, Yin *et al.* (18) used a non-targeted metabolomics approach (LC-MS) to identify novel biomarkers from plasma samples from 20 ACS patients and 20 non-ACS patients. Researchers found that phospholipid, glycolysis, and amino acid metabolism are altered in ACS patients compared with non-ACS patients. In 2021, Zhong *et al.* (19) applied a non-targeted LC-MS approach to plasma metabolomic analysis of 284 ACS patients and 130 healthy controls (HCs) to identify 28 metabolites that could be used to differentiate between the two groups. The receiver operating characteristic (ROC) curve showed that the combination of two metabolites, phosphatidylethanolamine lyso (16:0), and LPC (20:4), into one panel had an area under the curve (AUC) value of 0.905. In the same year, applying ultra-performance liquid chromatography coupled with the time of flight (UPLC-Q-TOF/MS) technique, Song *et al.* (20) examined serum samples from 45 ACS patients and 29 HCs and identified 46 differentially abundant metabolites. ROC curve analysis revealed that the three metabolites were used as diagnostic biomarkers with AUC values of 0.92–0.93. The diagnostic model constructed with metabolic biomarkers combined with cTNI had a high AUC value of 0.96. In 2024, Shibata *et al.* (24) also analyzed the metabolomic characteristics of 18 patients with ACS and 24 age-matched healthy volunteers by UPLC-Q-TOF/MS. A multiple logistic regression model for the diagnosis of ACS was established, in which the area under the ROC curve value of the lysine, isocitrate and tryptophan metabolite panel for distinguishing ACS patients from HCs was 1.00.

UA is the earliest type of disease process in ACS. In 2016, Ameta *et al.* (57) used 1H NMR to analyze serum samples from 65 patients with UA and 62 HCs. It was

found that the group of five metabolites, valine, alanine, glutamine, inosine, and adenine, was sufficient to achieve the maximum area under the ROC curve (AUC =0.99). In 2019, Wang *et al.* (58) examined serum samples of UA, unstable angina-diabetes mellitus (UA-DM), and HCs using the UPLC-Q-TOF/MS technique. First, 27 differential metabolites were identified by comparison of UA and HC. Pathway analysis showed that arginine and proline metabolism, glycerophospholipid metabolism, and purine metabolism were affected in patients with UA. Then, the authors applied metabolomics to detect UA and UA-DM metabolites and identified 22 differential metabolites. ROC analysis showed that six had high specificity and sensitivity for distinguishing UA from UA-DM, with AUC values above 0.85. Pathway analysis suggested that tryptophan metabolism is a key metabolic pathway in patients with UA combined with DM. In 2024, Hao *et al.* (64) used metabolomics to analyze serum samples from 33 UA, 38 myocardial infarction (MI) and 24 normal controls. The results revealed significant differences between MI and UA in xylene, hydroxycaproic acid, butylbenzene sulfonamide, octanetriol, phosphocholine and medronic acid. Pathway analysis showed that it was related to myocardial hypertrophy, Wnt signaling and fatty acid oxidation.

AMI is a serious threat to human health, because of persistent ischemia and hypoxia in the coronary arteries, which can cause myocardial necrosis and even death. In 2016, Fan *et al.* (25) applied the liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-Q-TOF/MS) technique to 1,086 blood samples [116 normal coronary artery (NCA), 276 non-obstructive coronary atherosclerosis (NOCA), 63 stable angina (SA), 307 UA, 324 acute myocardial infarction (AMI)] from center 1 for metabolomics. The results of the training set were validated by applying 933 blood samples from center 1 and 71, 68, and 166 blood samples from center 2, center 3, and center 4. The authors focused on the effects of NOCA versus NCA on plaque formation, SA versus NOCA on plaque growth, UA versus SA on the transition from stable to unstable coronary arteries, and AMI versus UA. A total of 89 differential metabolites were identified. Phospholipid catabolism was reduced, amino acid metabolism was increased, short-chain acylcarnitines were increased, the tricarboxylic acid cycle was reduced, and primary bile acid biosynthesis was reduced. The AUC values for the 12 metabolomics-specific biomarker-based experimental groups ranged from 0.938 to 0.996, providing 89.2% to 96.0% predictive values in the test phase and 85.3% to 96.4% predictive values in the 3-center outer set. In 2021, Aa *et al.* (26) applied GC-MS and LC-MS techniques to identify patients with AMI after the onset of chest pain versus patients with other cardiogenic chest pain (UA, myocarditis, heart valve disease) and combined the results of both methods and found that deoxyuridine (dU), homoserine and methionine could be potential biomarkers for AMI (AUC >0.91).

In the clinical setting, AMI is further classified into STEMI and NSTEMI based on the changes in the ST segment of the electrocardiogram. In 2015, Naz *et al.* (48) analyzed serum samples from 16 NSTEMI patients and 16 STEMI patients using CE-MS and identified 32 significant metabolites. Then, 13 carnitine-derived compounds and 13 amino acids were targeted and quantified in the serum of 20 STEMI patients and 28 NSTEMI patients using the HILIC-MS technique, and the c02-carnitine levels differed significantly between the two groups with an AUC of 0.85. Because it is crucial to examine left main coronary artery disease (LMCAD) before the occurrence of STEMI or sudden infarction death, in 2018, Huang *et al.* (49) examined serum samples including 44 STEMI patients (22 consecutive LMCAD and 22 non-LMCAD) using UPLC-MS technology. Fourteen metabolites were significantly different between LMCAD and non-LMCAD. ROC curve analysis showed that 9-cis-retinoic acid (9cRA) was the most important biomarker distinguishing the two groups with an AUC value of 0.888. Subsequently, the authors established a panel of 10 metabolites including 9cRA, dehydrophytosphingosine, 1H-indole-3-carbaldehyde, and 7 variants of lysophosphatidylcholine (LysoPC) with the largest AUC (0.933). In 2023, Luo *et al.* (55) applied a combination of metabolomics and OCT to detect the difference between plaque rupture (PR) and plaque erosion (PE). The results showed that docosahexaenoic acid (DHA), salicylic acid and proline were identified in both tests. ROC analysis showed that the areas under the curve of these metabolites in the training samples were 0.81, 0.70 and 0.67 respectively. The AUC values of 0.75, 0.73 and 0.74 were verified in the test samples.

Metabolomics-based prognostic biomarker analysis of ACS

The discovery of more novel biomarkers for early prognostic assessment of disease is essential to provide patients with more appropriate treatment strategies and further management (77). The 2023 ESC Management Guidelines emphasize the role of serial measurements of

high sensitivity cardiac troponin (hs-cTn) and consideration of changes in plasma brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations in the prognosis of ACS (78). One study found a substantial increase in the maximum chance of death in patients with elevated cardiac troponin T (cTnT) and cardiac troponin I (cTnI) (79). Another study showed that the NT-proBNP level at 6 weeks after ACS diagnosis was an independent predictor of future adverse outcomes. However, the predictive power of these biomarkers currently varies widely across disease endpoints, and the exploration of new prognostic biomarkers with high sensitivity and specificity is urgently needed (80).

Among the retrieved AMI studies, in 2019, Vignoli *et al.* (65) performed metabolomic analysis of serum samples from 80 surviving patients and 40 deceased patients, and for each serum sample, a nuclear Overhauser effect spectrum (NOESY) one-dimensional 1H-NMR spectrum was obtained. For each patient, a NOESY RF score was derived from the obtained NOESY spectrum, with the "RF risk score" indicating the extent to which the serum metabolomic profile appeared to be similar to that of one of the deceased patients. The metabolic profiles of 80 patients who survived and 40 patients who died were classified using the radio frequency (RF) classifier. The performance of the RF risk scores was compared with the actual results. The ROC analysis revealed an AUC of 0.859 for the NOESY spectrum, and the validation set (106 patients who died and 752 who survived) using the optimized NOESY RF risk score derived from the training set, the AUC value was 0.801. In 2022, Liu *et al.* (66) collected serum samples from 79 patients with AMI with cardiovascular disease (AMICVD), 28 of whom died within 1 year as the AMI with cardiovascular death (AMICVDD) group. A biomarker panel identifying three metabolites namely TMAO, OAG, and histidine was found to discriminate AMICVDD from AMICVD, and the AUC of this biomarker panel was 0.85 in the validation phase, which was the same as that in the discovery phase.

For NSTEMI and STEMI, there are also a number of previous articles that have identified valuable prognostic biomarkers. In Surendran *et al.*'s study (68) in 2019, a total of 108 plasma samples from 27 patients with STEMI were examined to identify changes in plasma metabolites during human ischemia/reperfusion (I/R) injury and to find potential plasma biomarkers to assess the extent of myocardial injury after PPCI. The researchers identified a panel of pentanoic acids, carnitine linoleate and choline 1-linoleate glycerophosphate as plasma biomarkers of severity with AUC values of 0.86. In 2021, Liu *et al.* (69) applied UPLC-MS technology to perform a metabolomic analysis of serum collected from 48 survivors (SSTEMI) and 48 non-survivors (DSTEMI). Twenty-six differential metabolites were identified, seven of which were strongly associated with the occurrence and different outcomes of STEMI. ROC curve analysis revealed multivariate linear support vector machine (SVM) algorithm and generalized estimating equation (GEE) model analysis of the panel consisting of seven metabolites with AUC values of 0.998 and 0.981, respectively.

For prognostic markers of ACS, many other researchers have applied cohort analysis. In 2016, Laaksonen *et al.* (70) studied the prognostic value of plasma ceramide (Cer) as a marker of cardiovascular death (CV death) in three independent coronary artery disease (CAD) cohorts. This finding was ultimately validated in a prospective Norwegian cohort study of patients with stable CAD, which demonstrated that ceramides, especially when used in proportion, are significantly associated with cardiovascular death. In the Corogene, SPUM-ACS, and BECAC studies, different plasma ceramide ratios were found to be important predictors of cardiovascular death in patients with stable coronary heart disease (CHD) and ACS. In 2023, Kraler *et al.* (71) recruited data from 2,619 ACS patients, follow-up for 30 days and 1 year, respectively, and mortality endpoints to observe whether changes in low-density lipoprotein (LDL) electronegativity are associated with adverse outcomes in patients with ACS. The results showed that changes in LDL electronegativity were associated with 30-day and 1-year all-cause mortality. It has replaced several risk factors that predict 1-year death.

Application of metabolomics to discover drugs for the prevention and treatment of ACS

ACS is most often caused by obstruction and requires the establishment of acute in-perfusion of blood flow. Currently, reperfusion is mostly achieved clinically with thrombolytic agents or percutaneous coronary intervention (PCI). Despite advances in treatment, the treatment and prognosis of ACS remain unsatisfactory, so new therapeutic approaches and medication targets are urgently needed (81). A list of the therapeutic effects and mechanisms of drugs for ACS are presented in *Table 5*.

Table 5 The therapeutic effect and mechanisms of drugs for ACS

No.	First author, year	Disease	Sample size	Source	Medicine	Mechanisms
1	Hu *et al.* (82), 2021	ACS	36 ACS-statins; 67 ACS	Serum	Statins	Statins modulated the gut microbiome of ACS patients towards a healthier status, reducing potentially pathogenic bacteria but increasing beneficial bacteria and specific changes in bacterial taxa were associated with disease severity or outcomes either directly or by mediating metabolites such as fatty acids and prenol lipids
2	Lam *et al.* (83), 2016	AMI	Antibiotic-treated rats; control	Plasma	Antibiotic	Researchers found that antibiotic treatment reduced intestinal microbial metabolites of the amino acids phenylalanine, tryptophan and tyrosine were associated with reduced severity of myocardial infarction
3	Liu *et al.* (84), 2014	AMI	6 control; 6 model; 6 positive; 6 XKS	Plasma	XKS	The results suggested that pretreatment of XKS protected metabolic perturbations in rats with MI, major via lipid pathways, amino acid metabolism and purine metabolism
4	Wu *et al.* (85), 2020	AMI	11 Sham; 11 Mod; 11 SJP-L; 11 SJP-H	Serum; tissue; urinary	SJP	Researchers indicated that the protective effect of SJP on cardiovascular disease was associated with systemic metabolic modulation, in particular regulation of amino acid and fatty acid metabolism
5	Wu *et al.* (86), 2020	AMI	11 Sham; 11 Mod; 11 SBP-L; 11 SBP-H	Serum; tissue; urinary	SBP	This study demonstrated that SBP was effective for protecting cardiac dysfunction by regulating amino acid, lipid and energy metabolisms
6	Tan *et al.* (87), 2012	AMI	7 Sham; 6 SND-treated	Urinary	SND	With the altered metabolism pathways as possible drug targets, we systematically analyze the therapeutic effect of SND, which demonstrated that SND administration could provide satisfactory effect on MI through partially regulating the perturbed myocardial energy metabolism
7	Yuan *et al.* (88), 2021	AMI	30 ω-3 therapy; 30 usual therapy	Plasma	ω-3	ω-3 PUFA supplementation may improve lipid metabolism and endothelial function possibly by affecting eicosanoid metabolic status at a systemic level during convalescent healing after AMI

ACS, acute coronary syndrome; AMI, acute myocardial infarction; PUFA, polyunsaturated fatty acid; SBP-H, Shexiang Baoxin Pill-high; SBP-L, Shexiang Baoxin Pill-low; SJP-H, Sukei Jiuxin Pill-high; SJP-L, Sukei Jiuxin Pill-low; SND, Sini decoction; XKS, Xin-Ke-Su.

Metabolomics-based study of ACS prevention through herbal medicine influenced metabolites

For the treatment of ACS, in addition to some therapeutic drugs, there are also some traditional Chinese medicines that play preventive roles in this disease. Xin-Ke-Su (XKS) is a patented drug that is extensively used in the treatment of ACS. In 2014, Liu *et al.* (84) established a myocardial infarction model after pretreating mice with different levels of XKS, and metabolomic analysis of serum samples from each group showed that XKS could protect rats from metabolic disorders through lipid pathways, amino acid metabolism, and purine metabolism thus protecting the cardiovascular system.

Using HPLC-Q-TOF-MS/MS technique, Wu *et al.* (85) examined body fluid samples from different groups of rats, which were rat models of acute myocardial infarction established by ligation of the left anterior descending branch of the coronary artery. This study demonstrated that Sukei Jiuxin Pills (SJP) achieve cardiovascular protection by regulating the metabolism of amino acids and fatty acids in the body. In the same year, Wu's team applied the same technique to study the action and analysis mechanism of Shexiang Baoxin Pill (SBP), and the results revealed that SBP protects the heart by regulating amino acid, lipid, and energy metabolism (86).

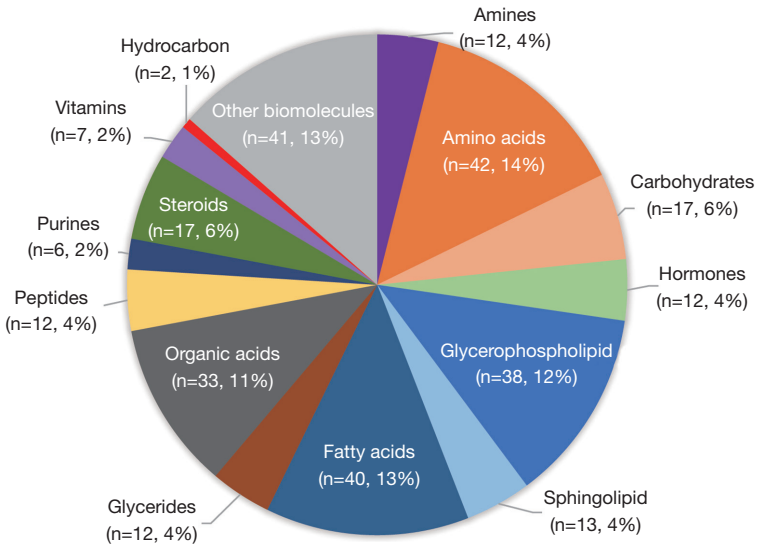

Figure 1 Type and number of acute coronary syndrome diagnostic biomarkers identified in the last decade.

Metabolomics-based study to treat ACS with drug-influenced gut microbial metabolites

According to previous studies, the microbiota and derived microbial compounds of the gut might play a positive role in human metabolism and may be relevant to the pathogenesis of some common metabolic diseases (89). Meanwhile, metabolites associated with gut microbes make important contributions to cardiovascular disease.

Hu *et al.* (82) applied 16SrRNA and untargeted UPLC-Q-TOF/MS techniques to samples from ACS patients with and without statin therapy to explore the mechanisms by which statins affect key gut microbes and metabolites for cardiovascular protection in ACS patients, and reported that statins modulate bacteria in the gut, and that gut bacteria modulate metabolites such as fatty acids and acrolein lipids to regulate disease severity.

On the other hand, Lam *et al.* (83) established a rat model in which multiple antibiotics were acted on rats after which feces, blood heart tissue were collected for testing, and the researchers found that antibiotic treatment reduced intestinal microbial metabolites of the amino acids phenylalanine, tryptophan and tyrosine were associated with a reduced severity of myocardial infarction.

Metabolomics-based metabolic pathway analysis of the major differential metabolites of ACS

Metabolic pathway analysis of ACS diagnostic biomarkers

We reviewed 50 articles applying metabolomics to detect diagnostic biomarkers of ACS in the last decade, of which 304 metabolites have been applied as diagnostic biomarkers. These metabolites can be categorized into ten groups, including amino acids, lipids, organic acids, hormones, carbohydrates, hydrocarbons, vitamins, purines, and amines. Lipids accounted for 29% of the metabolites, and can be subdivided into fatty acids (13%), glycerophospholipids (12%), and sphingolipids (4%). Amino acids account for 18% of which peptides account for approximately 4%. Organic acids accounted for 11%. Hormones account for approximately 10% of which steroids account for 6%. The percentages of other types of metabolites are shown in *Figure 1*. *Table 6* shows the metabolites found in ACS-related articles according to metabolite categorization ranked by the number of times they were mentioned in different articles.

There are 42 amino acid metabolites of which tryptophan (21%), glutamine (17%), isoleucine (14%), and alanine (17%) have been mentioned several times in several articles. Amino acid metabolites mainly regulate amino acid-related metabolic pathways in the body. Some also regulate the tricarboxylic acid cycle in the body. Tryptophan is associated with UA mainly regulates the tryptophan metabolic pathway in the body, which plays an important role in protein synthesis, endothelium-derived blood pressure control in stroke vessels, and microvascular inflammatory response (31). However, in addition to UA glutamine, isoleucine, and alanine have been associated with STEMI. Patients with AMI have increased serum levels of alanine,

Table 6 A list of diagnostic metabolites found in ACS related articles based on their classification

Classification	Metabolite	Disease	Reference
Amines	Choline	AMI, UA	(33,40,53,59,60,62)
	Betaine	AMI, ACS	(29,40,45,53)
	Trimethylamine oxide	UA, AMI	(45,59)
	Phosphorylcholine	AMI, ACS	(21,33)
	Isobutyryl-l-carnitine	ACS, AMI	(21,84)
Amino acids	Tryptophan	ACS, UA, AMI	(18,21,24,31,44,60,83,84,87)
	Glutamine	AMI, UA, ACS	(31,33,37,41,57,59,60)
	Alanin	AMI, STEMI	(21,31,33,43,50,57,87)
	Isoleucine/leucine	UA, AMI, STEMI	(33,40,41,50,54,59)
	Phenylalanine	UA, AMI	(33,40,43,59,60)
	Lysine	AMI, UA	(24,33,59,60)
	Valine	AMI, UA, STEMI	(33,54,57,59)
	Histidine	AMI	(33,34,41)
	Creatine	AMI, UA	(40,41,59)
	Glutamate	AMI, UA	(33,34,59)
	Proline	AMI	(40,55)
	Methionine	AMI	(26,43)
	Arginine	AMI	(40,42)
	Glycine	AMI	(50,87)
	Tyrosine	AMI	(33,83)
Carbohydrates	Inosine	STEMI, AMI	(31,40,57)
	Glycerol	AMI, STEMI	(31,50,53)
	myo-inositol	UA, AMI	(31,59)
Organic acids	Lactate	UA, AMI	(33,34,59,87)
	3-hydroxybutyrate	UA, ACS, AMI	(31,59,60)
	Citrate	AMI	(33,50,87)
	Pyruvate	AMI	(29,31,53)
	Citrulline	AMI, UA	(53,60)
	Hippuric acid	ACS, AMI	(21,87)
	Malic acid	AMI	(40,43)
	Succinate	AMI	(50,87)
Glycerophospholipid	Lysophosphatidylcholines	STEMI, AMI	(47,49,51,58)
	Glycerophosphocholine	AMI, UA, STEMI	(21,59,86)
	LysoPC(18:0)	AMI, ACS	(21,69,84)
	Glycerophospholipid	AMI	(32,39,46)
	LysoPC(16:0)	AMI	(38,84)
	LysoPC(18:2)	AMI	(38,84)

Table 6 (*continued*)

Table 6 (*continued*)

Classification	Metabolite	Disease	Reference
Sphingolipid	Dehydrophytosphingosine	STEMI, AMI	(49,52,69)
	Sphingomyelin	STEMI, AMI	(36,51)
	Phytosphingosine	AMI, UA	(62,84)
Purines	Hypoxanthine	AMI	(33,40,43)
	Uric acid	AMI	(40,53,84)
	Caffeine	AMI, ACS	(18,50)
Fatty acids	Linoleic acid	AMI	(30,38,39,84)
	Arachidonic acid	AMI	(30,38,39,84)
	Docosahexaenoic acid	AMI	(41,55,84)
	Palmitic acid	AMI	(36,50)
	Oleic acid	ACS, AMI	(18,50)
	α-linolenic acid	AMI	(30,43)

ACS, acute coronary syndrome; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

glutamine, histidine, valine, and isoleucine, suggesting that the tricarboxylic acid cycle (TCA) cycle is facilitated and may be supplied by these amino acids. Elevated levels of amino acids also indicate disruption of lipoprotein degradation and energy metabolism in patients with acute myocardial infarction (33). A total of 11 metabolites that can be categorized as peptides, including carnosine, histidinyl-valine, glutathione, and phenylalanyl-phenylalanine are mentioned in the article. Among them, phenylalanyl-phenylalanine and phenylalanyl-tryptophan are associated with the lipid peroxidation pathway of AMI (40).

Lipids can be classified as fatty acids, glycerophospholipids, or sphingolipids. Among fatty acids linoleic acid (10%) and arachidonic acid (10%) are mentioned in several articles. Both metabolites are associated with acute infarction and are involved in the fatty acid metabolic pathway of the body. The level of unsaturated fatty acids in the blood of AMI patients suggests that the large amount of lipids accumulating in the blood vessels may increase the risk of atherosclerosis (30). Some pharmacologic studies suggest that omega-3 polyunsaturated fatty acid supplementation during rehabilitation after AMI may improve lipid metabolism and endothelial function by modulating the arachidonic acid metabolic status (88). In addition, LysoPC has been suggested in several articles to be associated with ACS, and LysoPC activates a wide range of cell types in the vascular system, accelerating the evolution and progression of atherosclerosis by inducing cell proliferation, and increasing lymphocyte. Plaque formation and thrombus rupture, which are also related mainly to the ratio of LysoPC to lysophosphatidylethanolamine (LysoPE) in the blood (36). The most mentioned metabolite of sphingosine is dehydrophytosphingosine (17%), which can be used as a diagnostic and prognostic marker for AMI. It attenuates vascular inflammation or oxidative stress through different mechanisms, such as the activation of G protein-coupled receptors or peroxisome proliferator-activated receptors (49).

Thirty metabolites were classified as organic acids, and lactate (12%) and 3-hydroxybutyrate (9%) were identified several times in previous articles. As better diagnostic biomarkers for AMI and STEMI, elevated levels of 3-hydroxybutyrate and lactate consistently indicate impaired fatty acid oxidation, tissue hypoxia, and increased anaerobic glycolysis, and elevated plasma lactate levels in patients with acute myocardial infarction can vary according to the extent of injury (60). The carbohydrate group includes 18 metabolites, of which inosine, Myo-inositol, glucose have been identified in several articles, inositol, and glucose have been associated with AMI and can be used as diagnostic biomarkers of AMI. Serum glucose levels are higher in AMI patients than in control subjects, suggesting accelerated gluconeogenesis and altered anaerobic glycolysis. In addition, the serum levels of inosine, a purine degradation product involved in anaerobic glycolysis, are increased in

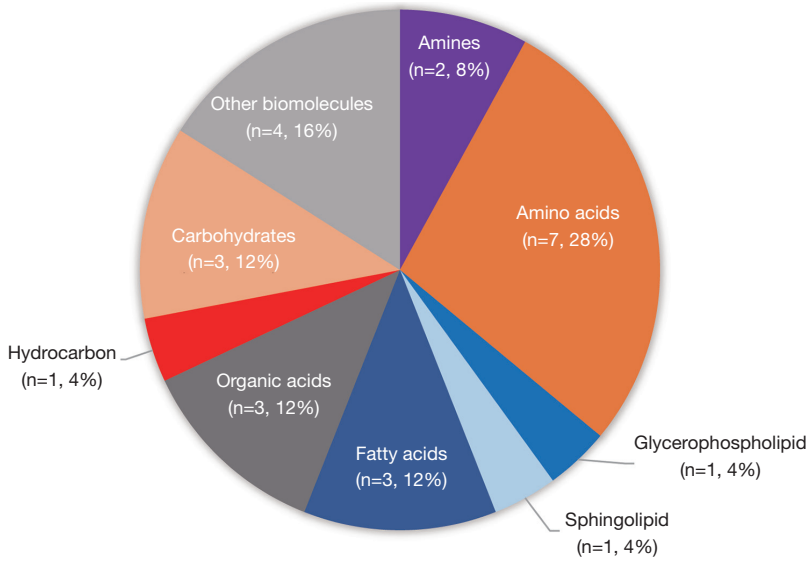

Figure 2 Type and number of acute coronary syndrome prognostic biomarkers identified in the last decade.

AMI patients, further confirming the observation of altered anaerobic glycolysis and energy metabolism (33).

Metabolic pathway analysis of ACS prognostic biomarkers

A total of 9 prognostic articles were mentioned in the article, and a total of 25 metabolites were found to be prognostic biomarkers of ACS. These prognostic metabolites can also be categorized into eight groups, including amino acids, lipid, organic acids, carbohydrates, hydrocarbons, and amines. Lipids accounted for 20% of the metabolites. Amino acids accounted for 28%, and organic acids accounted for 12%. The percentages of other types of metabolites are shown in *Figure 2*. *Table* 7 shows the metabolites found in ACS-related articles. Among the prognostic markers, the amino acid metabolites with the best proportions were mentioned, and histidine (29%) was mentioned in several articles. Previous study has found that histidine metabolism is closely related to the death outcome of AMI (66). L-histidine (HIS) can be synthesized by histidine decarboxylase. HIS also regulates the expression of histidases, produces uric acid, converts it to imidazoline propionate and hydrolyzes it to formiminoglutamate (FIGLU). The glutamate produced by FIGLU can be used to synthesize glutamine, which is eventually released into the blood. Researchers have reported elevated levels of histidine, glutamate, and glutamine in the event of eventual death from AMI (66).

The carbohydrate group included 3 prognostic metabolites, and two AMI prognosis-related articles identified mannitol as a potential prognostic marker. Mannose (67%) is responsible for maintaining the steady state of the blood and plays a central role in the glycosylation of lipoproteins involved in the development and progression of atherosclerosis. N-glycans are upregulated in a pro-inflammatory milieu and are found on the surface of endothelial cells during the early stages of atherosclerotic plaque formation. Authors reported that patients at high risk for AMI relatively high levels of mannose, suggesting that mannose binds relatively little to mannose-binding lectin (MBL), which reduces the activation of the lecithin pathway, one of the three modes of complement system activation (67).

Ceramide, a sphingomyelin metabolite among lipid metabolites, was mentioned in three articles as a prognostic marker for ACS. Researchers have reported that ceramides can promote a number of central atherosclerotic processes, including lipoprotein aggregation and uptake, inflammation, superoxide ion production, and apoptosis (70). High ceramide levels have also been found to be associated with cardiac cell death in a mouse model of myocardial infarction. In addition, ceramides can cause vascular dysfunction by inactivating endothelial nitrogen monoxide (NO) synthase (72).

Table 7 A list of prognostic metabolites found in ACS related articles based on their classification

Classification	Metabolite	Disease	Reference
Amines	Linoleoyl carnitine	STEMI	(68)
	TMAO	AMI	(66)
Amino acids	Histidine	AMI	(65,66)
	Glutamine	AMI	(66)
	Alanine	AMI	(66)
	Valine	AMI	(65)
	Creatine	AMI	(66)
	Proline	AMI	(65)
	Threonine	AMI	(66)
Lipids/fatty acids	Acetone	AMI	(65,66)
	Pentadecanoic acid	STEMI	(68)
	N-Acetyl-leukotriene E4	STEMI	(69)
Organic acids	N-acetylphosphinothricin	AMI	(66)
	3-hydroxybutyrate	AMI	(65)
	Formate	AMI	(65)
Carbohydrates	Mannose	AMI	(65,67)
	Inosine	AMI	(66)
	Myo-inositol	AMI	(66)
Lipid/sphingolipid	Ceramide	ACS	(70,72,73)

ACS, acute coronary syndrome; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TMAO, trimethylamine oxide.

Conclusions and future expectations

In conclusion, ACS is a common CAD, and although researchers have conducted metabolomic studies on ACS and successfully identified potential biomarkers for diagnosis, prognosis, and some pharmacological treatments, current studies have various shortcomings that need improvement.

In current studies on ACS, the maximum sample size collected in experiments is around 1,000 cases, but very few can reach this number, and most experiments have a sample size of a few hundred cases or even a few dozen cases. Therefore, in future studies, we can expand the sample size and collect multicenter samples, which will make the results more convincing. In addition, most of the current studies collected validation groups to verify the specificity and sensitivity of diagnostic and prognostic biomarkers, and several studies on AMI performed targeted metabolomics assays, however, they also targeted only one class of metabolites and did not target previously identified metabolite biomarkers. Therefore, in future studies, targeted metabolomics should be used more over to quantify previously identified valuable metabolites and to provide a more powerful account of the previous studies. Finally, we can also improve the accuracy of metabolite discovery by integrating metabolic data generated by different metabolic technologies, and we can also combine genomics and proteomics technologies to use multi-omics to better understand the regulatory networks among substances, to further understand the biological pathways and mechanisms of diseases.

It is believed that with the continuous advancement of technology and the efforts of millions of researchers, more accurate and specific markers will continue to emerge,

leading to greater breakthroughs in the diagnosis and prevention of ACS, thus improving the current status of ACS diagnosis and treatment.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-431/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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