

REVIEW

Perioperative metabolic phenotyping: emerging evidence and translational potential for risk stratification and anesthetic dosing

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Abstract

Metabolic phenotyping during the perioperative period, defined as the patient-specific characterization of metabolic activities across the pre-, intra-, and postoperative phases, is increasingly recognized as a promising component of emerging precision perioperative medicine, although it has not yet become an established pillar. It differs from conventional approaches based on static baseline assessments by capturing dynamic metabolic responses to surgical stress and anesthesia, which may enable more informative risk stratification than conventional assessment tools. Advances in metabolomics, pharmacometabolomics, and multiomics methodologies have enabled the identification of metabolic signatures associated with perioperative risk, medication responses, organ dysfunction, and recovery. This narrative review uses a structured search strategy in major databases (2015–2026) to synthesize current evidence regarding the utility, methodologies, and future potential of perioperative metabolic phenotyping in adults undergoing surgery. The review describes how studies were selected and critically evaluates the available evidence, emphasizing that most primary research consists of single-center observational cohort studies that require external validation. The review summarizes historical developments, mass spectrometry and nuclear magnetic resonance (NMR)-based techniques, and how these technologies are combined with artificial intelligence and pharmacogenomics to study anesthesia and intensive care outcomes. In addition, it collates clinical studies examining the associations between metabolic phenotypes and delirium, emergence agitation (EA), acute kidney injury, stress hyperglycemia, and organ dysfunction, and discusses pharmacometabolomic approaches to anesthetic drug selection and dosing. Finally, the review outlines key challenges to clinical adoption, including methodological heterogeneity, lack of external and interventional validation, economic and point-of-care barriers, and ethical and regulatory considerations, and highlights research priorities that must be addressed before perioperative metabolic phenotyping can evolve from exploratory research into a clinically robust decision support tool.

Keywords

Perioperative metabolic phenotyping; Pharmacometabolomics; Precision anesthesia; Multi-omics integration; Predictive metabolic biomarkers

1. Introduction

Major physiological and biochemical disturbances occur during the perioperative period as a result of surgery, anesthesia, inflammation, and hemodynamic changes. Surgery-induced metabolic alterations include increased catabolism, dysregulated glucose metabolism, and changes in amino acid and fatty acid metabolism. These metabolic alterations play a crucial role in determining postoperative outcomes, complications, and functional recovery [1]. The number of surgeries conducted annually around the globe was estimated to be approx-

imately 313 million in 2012. Even modest improvements in perioperative assessment could have substantial public health benefits [2].

However, complications such as acute kidney injury (AKI) and postoperative delirium (POD) remain major contributors to perioperative morbidity and mortality [3, 4]. AKI following major abdominal and cardiac surgeries is associated with prolonged hospital stay, greater intensive care unit (ICU) utilization, and mortality, whereas POD and postoperative cognitive dysfunction (POCD) have been associated with cognitive impairment, lower quality of life, and even institutionalization

[5, 6]. Conventional risk stratification models based on static clinical risk characteristics and routine laboratory parameters only partially capture these complex physiological changes.

Metabolomics, together with metabolic phenotyping, has been identified as a promising approach to enhance diagnostic accuracy, risk assessment, and the understanding of mechanisms in surgery and anesthesia [1, 7]. The measurement of small molecule metabolites in bodily fluids and tissues provides a snapshot of the current metabolic state, which is influenced by genetics, comorbidity, external factors, and acute physiological stress, unlike genomics, which measures only the genetic predisposition to develop certain conditions [7]. Moreover, pharmacogenomics has demonstrated the impact of genetic variants in enzymes and receptors involved in drug metabolism, such as cytochrome P450 variants and butyrylcholinesterase [8, 9]. Combining these approaches within a framework of precision anesthesia is considered crucial for contemporary perioperative care [10].

This narrative review offers an integrated analysis of perioperative metabolic phenotyping, focusing on: (1) analytical technologies and procedures; (2) perioperative metabolic markers and pathways; (3) pharmacometabolomics and anesthetic drug selection and dosing; (4) artificial intelligence (AI)-assisted and multi-omics-based risk stratification; and (5) implementation, regulatory, and health economic implications. We deliberately differentiate between topics that have accumulated sufficient evidence and those that remain in the early stages of investigation, drawing primarily on high-quality, peer-reviewed studies from the anesthesia and critical care fields and the metabolomics literature, in accordance with published recommendations for conducting narrative reviews in anesthesia and pain medicine [11].

2. Methodology

The present study is a narrative review designed to summarize significant advances in the field of perioperative metabolic phenotyping in adult surgical patients rather than a systematic review intended to comprehensively evaluate the available evidence. In accordance with current recommendations for conducting rigorous narrative reviews in anesthesia and pain management, the scope of this review is clearly defined, relevant data sources were identified, and a structured search strategy was conducted to minimize potential biases, while acknowledging the inherent limitation of narrative reviews [11].

2.1 Databases searched

Searches for relevant literature were conducted in PubMed, PubMed Central, Europe PMC, and leading anesthesia and intensive care journals, including the British Journal of Anaesthesia, Anesthesiology, Intensive Care Medicine, the Canadian Journal of Anesthesia, and Annals of Surgery, using combinations of controlled vocabulary and free-text keywords related to surgery, anesthesia, perioperative medicine, and metabolomics. The complete database-specific search strategy for each source is provided as **Supplementary Table 1**.

Embase and the Cochrane Library were not searched be-

cause the primary objective of this review was not to conduct a comprehensive systematic or scoping review but rather to provide a narrative analysis with an emphasis on key databases and relevant journals in anesthesiology and critical care medicine. Nevertheless, excluding Embase may have resulted in the omission of relevant studies, particularly those published in European journals. Accordingly, the findings presented in this review should be considered qualitative and hypothesis-generating rather than comprehensive.

2.2 Search strategy

("perioperative metabolomics" OR "perioperative metabolic phenotyping" OR "surgical metabolomics" OR "metabolic profiling surgery") AND ("anesthesia" OR "anaesthesia" OR "general anesthesia" OR "anesthetic dosing") AND ("risk stratification" OR "outcome prediction" OR "biomarker" OR "predictive model" OR "machine learning").

2.3 Eligibility criteria

To ensure the relevance of the evidence base, clear inclusion criteria were established. These criteria included: (1) peer-reviewed studies involving adult patients undergoing surgery during the perioperative period; (2) high-quality systematic reviews or narrative reviews; and (3) important methodological and regulatory guidelines relevant to the translational applications of perioperative metabolic phenotyping. Studies exclusively pediatric populations, those examining metabolism outside the perioperative context, preprints, conference papers without associated peer-reviewed full texts, industry publications, and those not specifically contributing to risk stratification or drug dosing were excluded. Given the rapid progression of the field, studies published from 2015 to 2026 were preferred, although highly influential landmark studies before this period were also considered. Given the rapid evolution of analytical techniques and perioperative research areas, priority was given to the most recent research from 2015 to 2026, although other studies prior to 2015 were included when necessary to provide background or elucidate the mechanisms behind certain phenomena.

2.4 Study selection and synthesis

Following title and abstract screening, potentially eligible articles underwent full-text review. Although Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were not explicitly applied for data extraction since the evidence synthesis was narrative, priority was given to studies that demonstrated methodological rigor, sufficient sample sizes, external validation, and clinical utility. The evidence base comprised 15 clinical studies, 16 reviews, and eight methodological papers. Overall, the clinical evidence base included in this review is relatively focused and should be regarded as providing a qualitative overview of perioperative metabolomics as a research field.

2.5 Summary of key clinical studies included in the evidence base

This review critically evaluated 15 primary clinical studies; a selected list of the most important studies along with their key biomarkers, analytical methods, and principal findings is provided in Table 1 (Ref. [8, 9, 12–19]).

2.6 Historical evolution of perioperative metabolic phenotyping

Historically, perioperative risk assessment has been based on clinical risk scores, comorbidity indices, and a limited number of biochemical markers such as creatinine, liver enzymes, and inflammatory mediators. Before the early 2000s, the metabolic alterations induced by surgery and anesthesia remained largely unexplored, primarily because of technical limitations in the simultaneous analysis of a large number of metabolites [1].

The development of high-resolution mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy substantially expanded metabolite coverage and improved the standardization of metabolomics analytical methods, thereby facilitating the early application of metabolomics in surgical populations. In this regard, Ghini *et al.* [19] (2015) demonstrated perioperative alterations in the plasma metabolome in patients undergoing colorectal surgery, reporting significant changes in energy, amino acid, and lipid metabolism during the perioperative period in patients undergoing colorectal surgery. Subsequent studies extended these findings to other types of surgery such as oncological and major abdominal surgery [12, 18].

More recently, a pilot mass spectrometry-based metabolomics study documented acute metabolic alterations across the perioperative period, illustrating the feasibility of serial sampling to characterize metabolic responses to surgery. However, this exploratory study did not evaluate whether longitudinal metabolic trajectories improved prediction of specific postoperative outcomes compared with single-time-point measurements [13]. Meanwhile, scoping reviews have emphasized the promise of metabolomics for diagnostic and prognostic applications in perioperative care but have also highlighted important limitations related to methodological standardization and external validation [1].

2.7 Principles and advantages of metabolic phenotyping

Metabolic profiling involves the comprehensive analysis of small molecules (metabolites) present in biological fluids and tissues, providing a snapshot of the integrated effects of genetics, physiology, environmental exposures, and disease processes at a particular time [7]. Unlike genomics, which provides information on a relatively static genetic makeup, metabolic signatures are highly dynamic and can change rapidly in response to factors such as surgery, anesthesia, and organ dysfunction.

The field of perioperative medicine may benefit from several theoretical strengths of metabolomics. First, it is capable of generating a biochemical signature of fundamental biological processes, such as metabolism, oxidative stress, immune re-

sponse, and organ function, which might help detect early signs of deterioration beyond those provided by traditional biomarkers [7, 16]. Second, it takes into account the interindividual biological variability that may be overlooked when using conventional risk scores [1]. Finally, integrating metabolomic data with clinical and other multiomics data facilitates the exploration of the underlying mechanisms through which surgical injury contributes to postoperative complications.

These features make metabolic phenotyping a potentially valuable addition to established risk assessment methods, particularly for complex multifactorial complications such as delirium, AKI, and stress hyperglycemia [3, 5, 6].

2.8 Analytical platforms and perioperative metabolomics workflow

Mass spectrometric (MS) and nuclear magnetic resonance (NMR) spectroscopy are the principal analytical platforms used in perioperative metabolomics [7]. High-resolution liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS) can detect a wide range of metabolite classes with high sensitivity and broad coverage, whereas triple quadrupole mass spectrometry (QqQ-MS) is well suited for quantitative targeted metabolomic analyses that can be applied clinically [7]. A comparison of the major analytical platforms used in perioperative metabolic phenotyping, along with their relative sensitivity levels, sample types, and other key analytical characteristics, is presented in Table 2.

In perioperative research, MS is commonly used in an untargeted manner to identify metabolic signatures, whereas NMR spectroscopy and targeted MS are primarily used to validate these findings and extend analyses to larger patient cohorts.

A typical perioperative metabolomic workflow involves sample collection, preparation, and analysis using standardized procedures that predefined sampling time points before, during, and after surgery to minimize sampling-related bias [7]. Extractive methods using organic solvents, such as methanol precipitation and methyl tert-butyl ether (MTBE) lipid extraction, are used to separate metabolites into polar and nonpolar fractions. Data acquisition using MS or NMR instruments incorporates internal standards and quality control samples to monitor analytical performance and instrument stability.

The raw data are analyzed using specialized software for peak detection, alignment, annotation, and normalization. Multivariate statistical analyses and machine learning techniques are subsequently employed to identify candidate biomarkers, elucidate metabolic pathways, and construct predictive models [20, 21]. Metabolomic datasets are increasingly integrated with clinical data and other omics datasets and other omics datasets (e.g., genomics and proteomics) within multi-omics frameworks, as further discussed later in this review.

TABLE 1. Selected pivotal primary studies included in the narrative evidence base on perioperative metabolic phenotyping.

Author (Year)	Study Design and Population	Analytical Platform	Key Findings and Biomarkers Identified	Methodological Strengths and Limitations
Krieg <i>et al.</i> [12] (2025)	Exploratory secondary analysis of RCT (TAPIR trial); N = 177; Adults undergoing major abdominal surgery	LC-MS (Targeted)	Perioperative depletion of primary amino acids (glutamine and serine) was associated with postoperative delirium and delayed recovery.	Strengths: Prospective RCT cohort, longitudinal sampling. Limitations: Secondary exploratory analysis, single-center data, trial not originally designed for metabolomics-guided management.
Seymour <i>et al.</i> [13] (2025)	Exploratory pilot study of adults undergoing surgery	Mass spectrometry-based metabolomics	Identified acute perioperative changes in metabolic profiles across serial sampling time points.	Small exploratory cohort; did not evaluate specific postoperative complications or compare predictive performance of longitudinal and single-time-point measurements.
Gegner <i>et al.</i> [14] (2024)	Methodological/Clinical Proof-of-concept	MTBE-SP3 (Multi-omics)	Demonstrated the feasibility of a single-sample workflow for simultaneous extraction of proteins and metabolites, facilitating multi-omics integration in perioperative settings.	Strengths: Highly resource-efficient, advanced multi-omics capability. Limitations: Technical proof-of-concept; requires validation in a larger clinical cohort.
Mi <i>et al.</i> [15] (2022)	Case-control; N = 51; Elective surgery under general anesthesia	Untargeted MS (Serum)	Identified 12 altered metabolites; vanillic acid, candoxatril, and decanoylcarnitine, that were associated with alterations in lipid and amino acid metabolism in EA.	Strengths: Strict 1:1.5 matching for age, sex, and surgery type. Limitations: Small sample size, untargeted approach requiring validation and absolute quantification.
Tripp <i>et al.</i> [16] (2021)	Nested matched case-control (SAGES cohort); N = 104; major non-cardiac surgery in older adults	Targeted MS	An 11-metabolite preoperative predictive panel achieved AUC of ~0.84 for postoperative delirium; the panel was associated with metabolites involved in branched-chain amino acids and the TCA cycle pathways.	Strengths: Well-phenotyped prospective geriatric cohort, matched design. Limitations: Lacks independent external multicenter validation.
Wang <i>et al.</i> [17] (2021)	Prospective observational; Adults under general anesthesia	Untargeted MS (Serum)	Preoperative markers (choline, cytidine, glycerophosphocholine, L-phenylalanine, oleamide, and inosine) strongly discriminated EA.	Strengths: High predictive discrimination (AUC approaching 1.0). Limitations: High risk of overfitting due to the lack of an external validation cohort.

TABLE 1. Continued.

Author (Year)	Study Design and Population	Analytical Platform	Key Findings and Biomarkers Identified	Methodological Strengths and Limitations
Mock-Ohnesorge <i>et al.</i> [18] (2021)	Prospective observational study; Pancreatic cancer surgery	LC-MS	Demonstrated significant perioperative alterations in the plasma metabolome during general anesthesia for pancreatic surgery.	Strengths: Detailed longitudinal intraoperative sampling. Limitations: Specific oncological population limits generalizability to benign surgeries.
Jhun <i>et al.</i> [8] (2019)	Clinical pharmacogenomic review/analysis of cohort data	Multi-platform	Highlighted how genetic variants (<i>e.g.</i> , <i>CYP2D6</i> , <i>CYP2B6</i>) require integration with real-time metabolic states for precision dosing.	Strengths: Comprehensive overview of perioperative medication metabolism. Limitations: Primarily relies on existing clinical databanks rather than novel prospective metabolomic discovery.
Wichmann <i>et al.</i> [9] (2016)	Pharmacogenomics/metabolomics observational study; patients undergoing neuromuscular block	Genetic sequencing/Enzymatic assay	Identified novel mutations in the butyrylcholinesterase (<i>BCHE</i>) gene that explained prolonged effects of succinylcholine.	Strengths: Direct clinical pharmacodynamic link to specific enzyme mutations. Limitations: Small targeted genetic cohort; lacks broader untargeted metabolomic context.
Ghini <i>et al.</i> [19] (2015)	Prospective observational study; Colorectal cancer surgery	NMR Spectroscopy	Documented perioperative metabolic responses to surgical stress and anesthesia, focusing on shifts in energy, lipid, and amino acid metabolism.	Strengths: Seminal study establishing baseline anesthesia/surgical metabolomic shifts. Limitations: Did not correlate signatures with long-term adverse clinical outcomes.

RCT, Randomized Controlled Trial; *TAPIR*, Targeted Perioperative Inflammatory Response (trial); *LC-MS*, Liquid Chromatography–Mass Spectrometry; *MTBE-SP3*, Methyl Tert-Butyl Ether–Single-Pot Solid-Phase-Enhanced Sample Preparation; *MS*, Mass Spectrometry; *EA*, Emergence Agitation; *SAGES*, Successful Aging after Elective Surgery; *AUC*, Area Under the Receiver Operating Characteristic Curve; *TCA*, Tricarboxylic Acid (cycle); *CYP2D6*, Cytochrome P450 Family 2 Subfamily D Member 6; *CYP2B6*, Cytochrome P450 Family 2 Subfamily B Member 6; *NMR*, Nuclear Magnetic Resonance.

TABLE 2. Comparison of analytical platforms for perioperative metabolic phenotyping.

Platform	Sensitivity	Coverage	Quantification	Sample types	Throughput	Key advantages
LC-MS/GC-MS	High	Broad	Semi/absolute	Plasma, urine, tissue	Moderate	High sensitivity, wide coverage
QqQ-MS	Very high	Targeted	Absolute	Plasma, serum, urine	High	Quantitative, robust, scalable
NMR spectroscopy	Moderate	Moderate	Absolute	Plasma, urine	High	Non-destructive, highly reproducible

LC-MS, Liquid Chromatography–Mass Spectrometry; GC-MS, Gas Chromatography–Mass Spectrometry; QqQ-MS, Triple Quadrupole Mass Spectrometry; NMR, Nuclear Magnetic Resonance.

Quality assurance is essential for any clinical application. The Metabolomics Standards Initiative (MSI) has published guidelines for standardizing experimental procedures and minimal reporting requirements, whereas Strengthening the Reporting of Observational Studies in Epidemiology–Molecular Epidemiology (STROBE-ME) provides reporting guidelines for metabolomics studies in molecular epidemiology based on the STROBE statement [7, 22]. Perioperative metabolomics studies that follow these guidelines are more likely to produce reproducible findings, and facilitate future clinical translation.

2.9 Perioperative metabolic biomarkers and pathways

Several perioperative studies have identified characteristic alterations in perioperative periods that have shown some characteristic alterations in the amino acids, purine, lipid, energy, and oxidative stress pathways during surgery [12, 16].

Among these metabolite pathways, amino acid metabolism is of special importance. Altered postoperative levels of glutamine, serine, citrulline, alanine, asparagine, and tyrosine have been associated with postoperative delirium, immune response, and postoperative recovery in patients undergoing major surgery [12, 23]. Disturbances in the levels of these amino acids may reflect metabolic stress, alteration in protein synthesis, and intestinal or hepatic dysfunction. Alterations in purine and pyrimidine metabolism are another important factor, with disturbances in the levels of inosine, hypoxanthine, and uric acid proposed as potential markers of oxidative stress [17, 24].

Alterations in lipid metabolism, reflected by changes in glycerophosphocholine, oleamide, and linoleic acid derivatives, have been observed in studies of emergence agitation and postoperative cognitive outcomes [17]. Alterations in energy metabolism, including changes in lactate, pyruvate, and tricarboxylic acid (TCA) cycle metabolites, suggest altered mitochondrial energy function among postoperative patients who exhibit complications [13, 16]. Although postoperative acute kidney injury is a clinically important complication, perioperative metabolomic studies in adult surgical populations have focused predominantly on outcomes other than acute kidney injury; therefore, evidence specifically addressing acute kidney injury remains limited [1]. Despite AKI being one of the most common complications during surgery and a key concept within metabolic phenotyping, there was only very little perioperative metabolomics data available regarding AKI

in adults undergoing surgery. The majority of metabolomic data regarding AKI was found in general critical care studies or among other patient populations, meaning that these data were not eligible for inclusion in the present review. Thus, the biomarkers and pathways described below have been mostly studied in the context of neurocognitive function, emergence agitation, metabolic response to stress, and infection. An illustration showing interactions between amino acid, purine, lipid, energy, and oxidative stress pathways and their potential role in perioperative complications and recovery is presented in Fig. 1 below.

2.10 Clinical evidence and predictive value

The body of literature examining the association between perioperative complications and metabolic phenotypes has expanded significantly in recent years, despite considerable heterogeneity and limited external validity.

In the context of emergence agitation (EA), Wang *et al.* [17] (2021) conducted preoperative serum metabolomic profiling in adults undergoing general anesthesia to compare metabolic profiles in patients with and without EA. Six metabolites were identified as potential candidates for differentiating between these two conditions, namely choline, cytidine, glycerophosphocholine, L-phenylalanine, oleamide, and inosine. The area under the Receiver Operating Characteristic (ROC) curve (AUC) for all six metabolites approached 1.0 within the study cohort [17]. Such near-perfect discrimination in a small derivation cohort, especially in a single center, may indicate overfitting and optimism bias rather than genuine biological discrimination of a multifactorial clinical outcome such as emergence agitation. Similarly, Mi *et al.* [15] (2022) demonstrated associations between several lipid and amino acid metabolites in postoperative serum and emergence agitation.

Specifically, regarding delirium and cognitive status, Tripp *et al.* [16] (2021) used targeted metabolomic profiling in older adults enrolled in the Successful Aging after Elective Surgery (SAGES) cohort and identified distinct preoperative and postoperative metabolic signatures related to postoperative delirium, especially in relation to branched-chain amino acids and TCA cycle intermediaries. Other studies have reported serum metabolic signatures that can predict preoperative and postoperative cognitive impairment, with some studies developing machine learning algorithms that achieved AUC values greater than 0.9 for predicting perioperative cognitive decline in elderly patients undergoing surgery [25, 26].

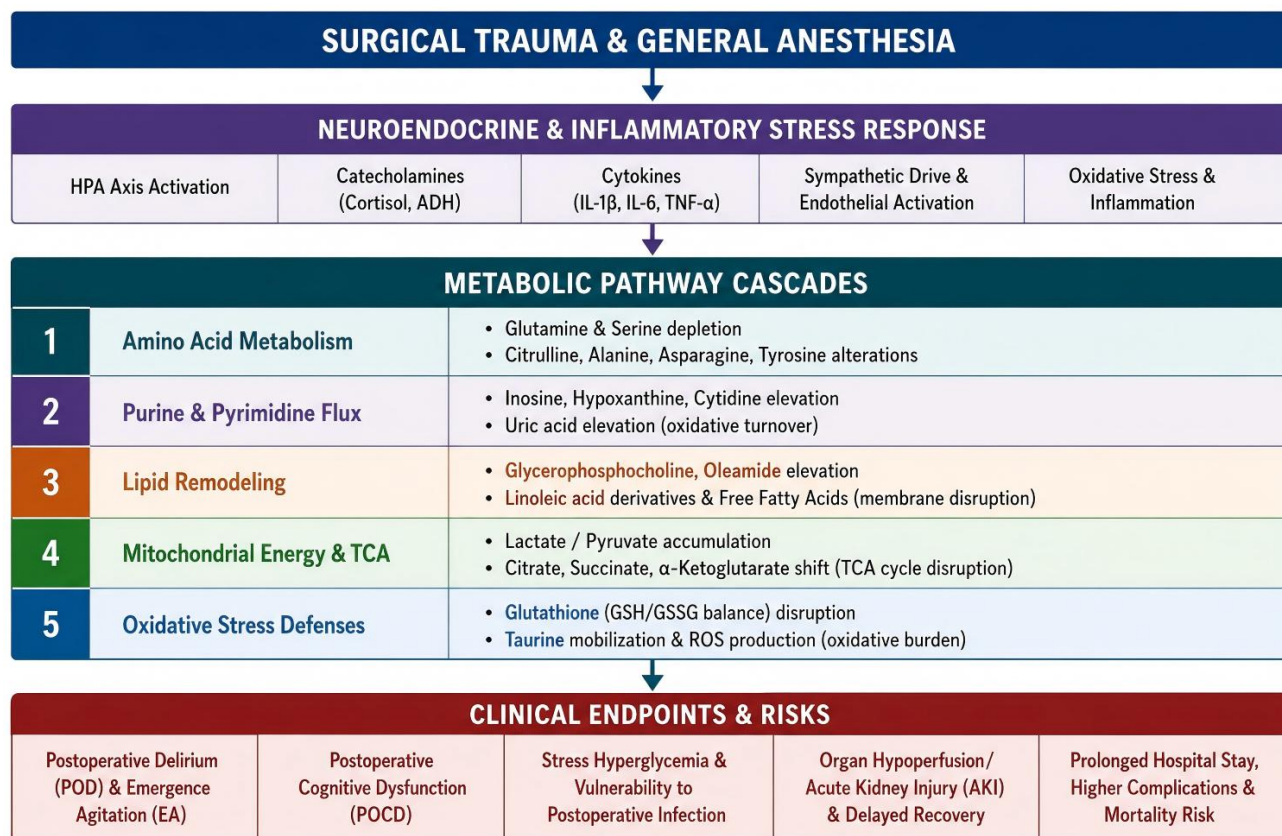


FIGURE 1. Metabolic pathway involvement in perioperative complications. HPA, Hypothalamic–Pituitary–Adrenal (axis); ADH, Antidiuretic Hormone; IL, Interleukin; TNF, Tumor Necrosis Factor; TCA, Tricarboxylic Acid (cycle); ROS, Reactive Oxygen Species.

In patients undergoing major abdominal surgery, Krieg *et al.* [12] (2025) observed that the perioperative decrease in the plasma concentrations of amino acids, including glutamine and serine, was associated with postoperative delirium and delayed recovery. This paper is thus a second-level exploratory metabolomic analysis of a randomized clinical trial and not an assessment of whether the Targeting preoperatively Assessed Personal Cardiac Index in major abdominal suRgery patients (TAPIR) study used of metabolomics to guide perioperative care as an intervention. In cardiac surgery, longitudinal studies of metabolomics have characterized metabolic trajectories in association with stress hyperglycemia and infections, supporting a trajectory approach in studying vulnerability and resilience [13]. Some key results from these and other selected perioperative metabolomics studies, alongside their corresponding clinical implications, are shown in Table 3 (Ref. [12, 15–17, 23, 26]) below.

In summary, the outcomes of the reviewed studies suggest the potential utility and applicability of metabolomics as a tool for perioperative risk stratification, particularly in the context of neurocognitive dysfunction and metabolic disease. However, the reality that most of the proposed models are developed using data collected from single-center studies and have not undergone external or multicenter validation means that their outcomes should be considered preliminary. Without independent validation in external multicenter cohorts, their discriminatory power cannot be generalized beyond the initial study sample sizes and should not be used to make treatment

decisions in clinical practice [1, 20]. Notwithstanding the high discriminatory performance reported in some studies, the existing literature is predominantly based on single-center observational or case-control studies without external validation.

Although postoperative acute kidney injury (AKI) remains a clinically important complication, relatively few studies have investigated perioperative metabolomic profiling of AKI in adults undergoing surgery. Moreover, the available studies have not yet identified biomarker panels that have undergone external validation, and therefore the current evidence was considered insufficient for inclusion in this review.

2.11 Pharmacometabolomics and anesthetic drug dosing

Pharmacometabolomics integrates metabolomics with pharmacokinetic and pharmacodynamic principles through the use of baseline and longitudinal metabolic datasets to characterize interindividual variability in drug response [27]. While pharmacogenomics examines genetic determinants of drug metabolism and receptor activity, pharmacometabolomics provides real-time insights into organ function, comorbidities, environmental factors, and their impact on drug metabolism [8, 27].

In anesthesiology, pharmacometabolomics has considerable potential for optimizing the dose of certain medications such as propofol, opioids, and neuromuscular blockers, because substantial interindividual variability exists in drug clearance

TABLE 3. Selected perioperative metabolomics studies and associated outcomes.

Study/condition	Key findings	Clinical implication
Major abdominal surgery	Amino acid depletion predicts delirium and slower recovery [12]	May suggest promising targets for nutritional interventions
Non-cardiac surgery (older adults)	Metabolite panels predict delirium [16, 23]	May aid in the early identification of high-risk patients
General anesthesia (EA)	Pre- and postoperative metabolic signatures predict EA [15, 17]	Potential for risk-based prophylaxis and monitoring
Older adult surgical patients	Preoperative Serum metabolites predict perioperative cognitive decline [26]	Candidate metabolic markers require validation before clinical use

EA, emergence agitation.

and pharmacodynamic response [28]. Metabolite biomarkers of hepatic and renal dysfunction, including altered bile acid profiles, amino acid imbalances, and uremic toxins, may facilitate dose optimization for drugs metabolized by the liver or excreted by the kidneys [29, 30]. A comparison of the distinct yet complementary roles of pharmacogenomics, pharmacometabolomics, and multi-omics approaches in guiding anesthetic dosing is presented in Table 4.

Several recent studies have integrated pharmacogenomics and metabolomics data to develop pharmacometabolomic models of propofol pharmacokinetics and opioid responsiveness [10, 31]. Similarly, greater insight into the increased susceptibility to succinylcholine-induced neuromuscular blockade in individuals with genetic variants in the butyrylcholinesterase (*BCHE*) gene can be gained through metabolomic profiling of cholinesterase activity and related metabolic pathways [9]. Currently, pharmacometabolomics-guided anesthetic dosing remains at the research and proof-of-concept stage; there are no clinical trials demonstrating that pharmacometabolomics-guided dosing improves perioperative outcomes or safety compared with standard dosing strategies. Accordingly, pharmacometabolomics should presently be viewed as a mechanistic and hypothesis-generating tool rather than a basis for routine adjustment of anesthetic dosing in clinical practice.

2.12 Multi-omics integration and AI-enabled prediction

Perioperative risk and variability in drug response can be investigated across multiple biological layers, including genomics, transcriptomics, proteomics, and metabolomics. The aim of multi-omics approaches is to integrate data from these biolog-

ical layers to provide a more comprehensive understanding of biological systems [31, 32]. Metabolomics is often regarded as the downstream phenotype that reflects the cumulative effect upstream biological processes and environmental factors on the patient.

Recent technological advances have enabled single-sample workflows that simultaneously extract proteins and metabolites from the same patient sample, for example, as described by Gegner *et al.* [14] (2024) with the methyl tert-butyl ether–single-pot solid-phase-enhanced sample preparation (MTBE-SP3) method. This workflow is particularly valuable in the perioperative setting, where patient samples are often limited in volume and are collected repeatedly.

Machine learning algorithms are particularly well suited for analyzing multi-omics data [21]. For example, random forest classifiers, support vector machines, and deep neural networks have shown considerable promise for predicting perioperative delirium, perioperative infections, acute kidney injury (AKI), and postoperative cognitive dysfunction, often demonstrating superior predictive performance than traditional regression models [16, 20, 24]. Model interpretability methods, such as SHapley Additive exPlanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME), help identify the metabolites and clinical variables or patient characteristics that contribute most to perioperative risks and are therefore support model evaluation and potential clinical implementation [21].

A Conceptual framework for the integration of genomic, proteomic, and metabolomic data with artificial intelligence-driven models for the assessment of perioperative risks and dosing recommendations is presented in Fig. 2.

Although these models show considerable promise, they

TABLE 4. Integration of pharmacogenomics and pharmacometabolomics in anesthetic dosing.

Approach	Key features	Clinical application
Pharmacogenomics	Genetic variants (e.g., <i>CYP2D6</i> , <i>CYP2B6</i> , <i>BCHE</i>)	Predicts enzyme activity, informs drug choice and baseline dose
Pharmacometabolomics	Baseline/dynamic metabolite profiles	Reflects real-time organ function and metabolism, supports dose adjustment
Multi-omics	Combined genetic and metabolic data	Enables comprehensive risk and dosing models

CYP2D6, Cytochrome P450 Family 2 Subfamily D Member 6; *CYP2B6*, Cytochrome P450 Family 2 Subfamily B Member 6; *BCHE*, Butyrylcholinesterase (gene).

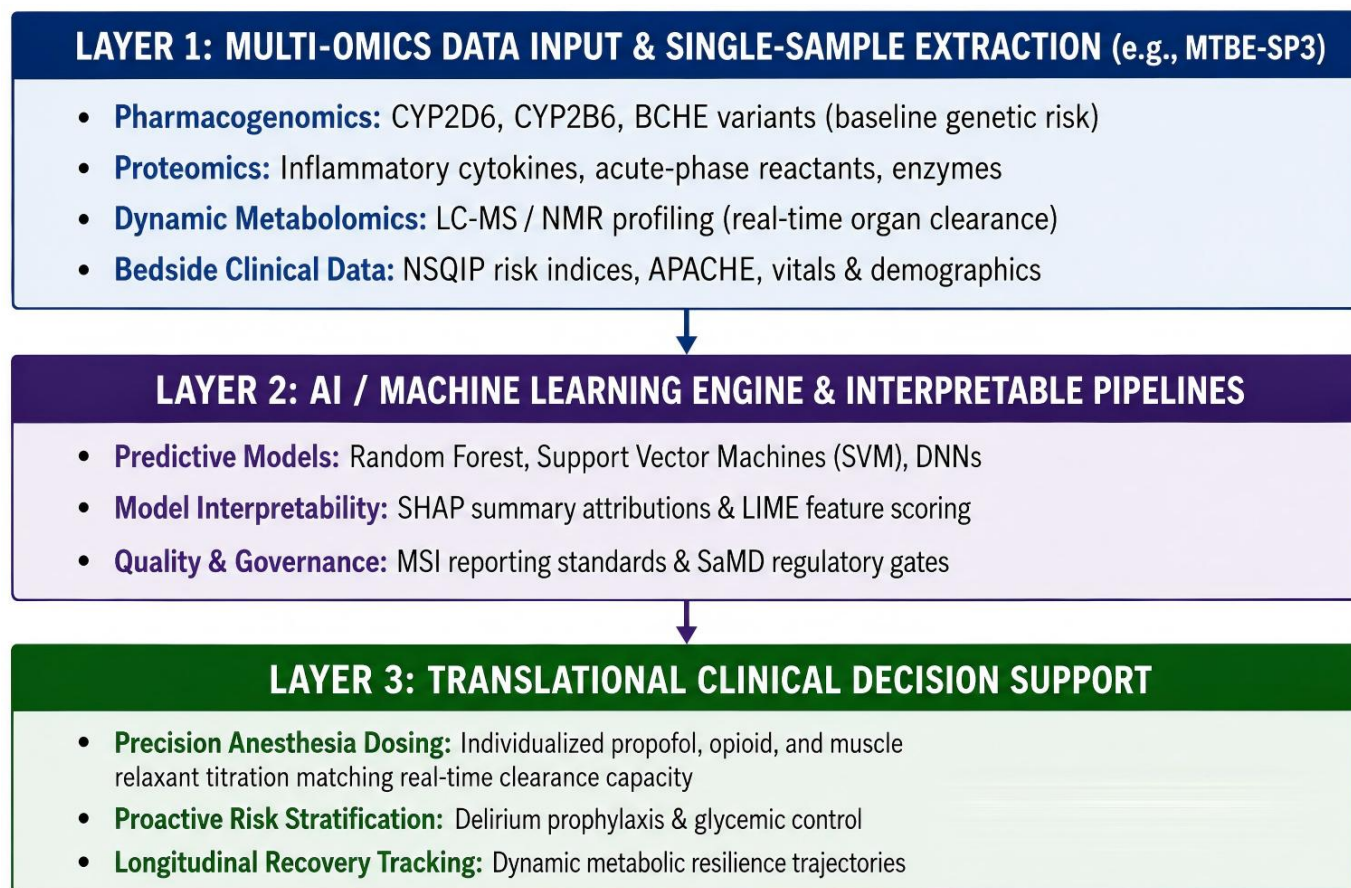


FIGURE 2. Multi-omics integration framework for perioperative risk stratification and precision anesthesia. MTBE-SP3, Methyl Tert-Butyl Ether–Single-Pot Solid-Phase-Enhanced Sample Preparation; *CYP2D6*, *Cytochrome P450 Family 2 Subfamily D Member 6*; *CYP2B6*, *Cytochrome P450 Family 2 Subfamily B Member 6*; *BCHE*, *Butyrylcholinesterase (gene)*; LC-MS, Liquid Chromatography–Mass Spectrometry; NMR, Nuclear Magnetic Resonance; NSQIP, National Surgical Quality Improvement Program; APACHE, Acute Physiology and Chronic Health Evaluation; AI, Artificial Intelligence; DNNs, Deep Neural Networks; SHAP, SHapley Additive exPlanations; LIME, Local Interpretable Model-Agnostic Explanations; MSI, Metabolomics Standards Initiative; SaMD, Software as a Medical Device.

have largely been developed using data from single-center studies and lack external validation. Furthermore, regulatory pathways for artificial intelligence (AI)-based Software as a Medical Device (SaMD) continue to evolve [20].

2.13 Implementation, regulatory, ethical, and economic considerations

The clinical implementation of perioperative metabolomics would involve considerations such as assay validation, regulatory categorization, ethical considerations, and health economics. Assay validation should demonstrate reliability, reproducibility, sensitivity, specificity, and stability of the metabolic profile before clinical application, especially when test results will be used for decision-making, such as triaging or dosing [7]. For clinical validation, it is necessary to demonstrate that the biomarker or model adds value to diagnosis, risk stratification, or decision-making [20, 33].

If metabolomics-derived tools are incorporated into AI-enabled clinical decision-support systems, their clinical implementation would require appropriate analytical validation, clinical validation, transparency, and post-

deployment performance monitoring.

For AI-powered metabolomic tools, implementation may require compliance with Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulations governing SaMD, which include rigorous analytical validation, clinical performance, generalizability across multiple sites, ongoing post-market surveillance, and clear model update procedures. In practice, this represents a considerable barrier to entry for perioperative AI-metabolomics tools, considering the limited sample size and single-center cohorts currently used in this field.

Ethical and data governance considerations include obtaining appropriate informed consent for metabolomics and other omics analyses, ensuring strong privacy protection for the high-dimensional personal data involved, and responsible data sharing in accordance with databases like Metabolights [22, 34]. Since omics data are highly unique and may enable patient re-identification even after traditional anonymization techniques, privacy concerns go beyond the privacy challenges posed by traditional clinical laboratory data. Privacy protections should therefore extend beyond encryption and access control measures; governance models and privacy-preserving

analytics may also be needed, especially when sharing raw omics data across organizations. Given the potential for patient re-identification from omics data, appropriate safeguards are therefore essential.

From an economic perspective, the adoption of metabolic phenotyping involves substantial upfront and ongoing costs, including high-end mass spectrometry or NMR platforms, specialized laboratory infrastructure, dedicated technical staff, and advanced data management and analytics capabilities. These requirements are particularly challenging for resource-limited hospitals and for perioperative services without on-site metabolomics laboratories. Although preliminary health economic evidence suggests that better risk stratification and prevention of adverse events in high-risk surgical populations might be cost-effective or even cost-saving if metabolomics were to be embedded into existing perioperative pathways, no formal perioperative cost-utility models or budget impact analyses specific to metabolomics-guided care are currently available. As a result, the true affordability and scalability of perioperative metabolomics remain uncertain, especially outside tertiary academic centers [33].

Nevertheless, the greatest challenge for clinical adoption at present is probably the absence of reliable point-of-care platforms for metabolomics analysis because current platforms remain slow and centralized, limiting their ability to support timely decisions during surgery.

3. Discussion

This review article highlights the rapid advancement of perioperative metabolic phenotyping and its potential application to enhance personalized and mechanistic perioperative management. Over the past decade, metabolomics research in perioperative medicine has evolved from simply describing perioperative biochemical alterations to creating candidate biomarker panels and predicting outcomes such as perioperative delirium, EA, AKI, stress hyperglycemia, and infection [1, 12, 16, 17]. Metabolomic profiles have proven useful prognostic additions to existing clinical scores across different settings, particularly in neurocognitive disorders and complex metabolic dysfunctions. Nevertheless, at this point, it is important to consider metabolomics-based approaches promising from a conceptual perspective but still premature for routine clinical translation, in light of the preponderance of single-centre observations and the lack of randomised intervention trials demonstrating patient benefit, together with a relative lack of validation.

Similarly, the newly developed perioperative metabolomics biomarker panels should be interpreted in the context of well-established clinical prediction tools already widely used, including the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) Surgical Risk Calculator for perioperative complications and mortality and ICU scoring systems like Acute Physiology and Chronic Health Evaluation (APACHE) for ICU mortality. In contrast to these scoring systems, which integrate demographic characteristics, comorbidities, surgical variables, and bedside physiological measurements, the metabolomics panel captures information regarding the biochemical response of patients to perioperative stress, injury, and

neuroinflammation. To date, few studies have directly compared newly developed perioperative metabolomics panels with ACS NSQIP, APACHE, or other established predictive models, and no prospective trials have demonstrated that the addition of metabolomics data provides incremental predictive value over these established methods. Thus, at present, perioperative metabolomics should be considered a promising adjunct to traditional risk assessment, rather than a replacement. Pharmacometabolomics represents an emerging area of research by examining how individual metabolic profiles influence anesthetic drug metabolism and therapeutic response, particularly when integrated with pharmacogenomics and clinical data [10, 27, 28]. Theoretically, such an interdisciplinary approach could minimize under- or overmedication during anesthesia, reduce adverse drug effects, and individualize neuromuscular blockade and pain relief, but robust clinical evidence is still lacking.

The combination of metabolomics with proteomics, genomics, and AI-driven models has further expanded the scope of perioperative phenotyping [14, 17, 32]. Multi-omics profiling from single samples combined with interpretable AI algorithms offers a promising pathway for developing clinically actionable multi-omics risk prediction and dosing guidelines. However, most studies of multi-omics in perioperative medicine continue to rely on relatively small cohorts, and the high AUC values close to 1.0 observed in derivation cohorts should be interpreted cautiously due to risks of overfitting and optimism bias [1, 20]. These AI-driven multi-omics models should therefore be regarded as early-stage exploratory tools that illustrate potential future directions rather than evidence-based clinical decision-support systems at present.

One particularly promising theoretical advancement of perioperative metabolomics is its focus on dynamic metabolic profiles and physiological resilience, rather than solely on static risk factors. Patients with stable metabolic profiles or a rapid return to a stable state following surgery have lower chances of experiencing complications, while those with prolonged metabolic dysregulation may indicate susceptibility to adverse events [12, 13]. The integration of dynamic metrics in perioperative monitoring may enable more precise risk stratification and early intervention, but it will necessitate rapid and standardized testing procedures as well as validated clinical decision-making tools.

4. Critical appraisal of the evidence base

As rapid progress continues in the field of perioperative metabolic phenotyping, careful examination of the existing literature highlights several important methodological limitations in the current evidence base. Clinical studies are predominantly observational and conducted in single centers with small-to-moderate-sized cohorts [20, 25]. Accordingly, the current evidence base should be regarded as exploratory and hypothesis-generating rather than sufficiently robust. The risk of selection bias is substantial, reducing the generalizability of the identified biomarkers. In addition, comparisons across studies remain challenging due to differences in study design, particularly with respect to

bio-sample timing, analytical platforms (NMR and mass spectrometry), and bioinformatics approaches [7, 22]. Lack of standardized sample collection protocols throughout the perioperative period, together with differences in bioinformatics pipelines used for data normalization, further contributes to methodological heterogeneity. Many studies in this field are also limited by having small to moderate sample sizes with study designs, such as case-control studies involving 50–100 participants or nested cohorts including more than 100 occurrences. Such limitations become especially critical for building multivariate machine learning prediction algorithms or multiple-metabolite profiles, as there can be an overabundance of variables in comparison with the number of cases, making it easy to discover false associations and rendering the results unstable. Furthermore, few existing preoperative metabolomics studies calculate a power analysis prior to performing high-dimensional metabolomic profiling, which further reduces confidence in the validity of the reported findings. Therefore, at present, such models should be considered exploratory and should be confirmed in other prospective cohorts with sufficient statistical power.

Notably, much of the existing literature reporting excellent predictive performance, including AUC values approaching 1.0, remains unvalidated in an external cohort setting and is therefore vulnerable to overfitting and optimism bias. Without external validation in independent samples, preferably from multisite settings, these models will be considered exploratory rather than ready for clinical implementation. Most published studies have employed a hypothesis-generating observational framework, or secondary analysis of pre-existing cohorts, limiting causal inference regarding perioperative metabolic pathways. The current evidence base is therefore largely hypothesis-generating rather than confirmatory. At present, few, if any, prospective randomized intervention studies have demonstrated improved clinical outcomes with metabolomics-guided management compared with standard care [32, 35]. As such, perioperative metabolomics currently represents a valuable tool for demonstrating biological plausibility, risk enrichment, and the development of testable mechanistic hypotheses; however, there is still insufficient data to recommend changes to clinical practice based on it. Metabolomics analysis may be difficult to interpret since metabolites are involved in overlapping pathways, requiring additional data from proteomics and genomics.

However, clinical implementation of these multidimensional technologies remains challenging. It is essential to develop intuitive clinical decision-support interfaces for anesthesiologists and surgeons that can translate metabolomics information into meaningful and actionable insights, alongside clinical thresholds and decision rules that demonstrate added predictive or clinical value compared to conventional treatments [33, 35]. These thresholds and decision rules will need to be derived and validated in multicenter prospective cohorts and, ultimately, evaluated in randomized interventional trials. Finally, data privacy, ethical governance, and regulatory oversight of multi-omics data and AI-based SaMD must also be addressed.

Furthermore, many studies have focused on narrowly defined surgical populations like pancreatic cancer surgery, ma-

jor abdominal surgery, cardiac surgery, or very old age patients; thereby limiting the generalizability of their findings to more heterogeneous perioperative surgical patients. Also, most of the study cohorts used are from geographically and demographically homogeneous populations with little diversity in terms of various genetic, lifestyle, and other medical conditions of patients that affect their metabolic characteristics; despite well-established evidence that metabolic profiles vary according to genetics, lifestyle, environmental, and disease-related factors.

5. Future directions

Implementation of perioperative metabolic phenotyping in clinical practice will require coordinated efforts across methodological, clinical, regulatory, and economic domains. From a methodological standpoint, it is essential to establish standardised protocols for sample preparation, analysis, and interpretation of perioperative metabolomics data, guided by MSI and STROBE-ME recommendations [7, 22]. Collaborative efforts should include standardized sampling protocols and participation in external quality assurance programs. Beyond following established reporting standards, consensus is needed regarding standardized sampling windows during the perioperative period, optimal analytical technologies for specific clinical questions, and harmonized bioinformatics pipelines to reduce methodological heterogeneity and facilitate comparisons across studies.

From a clinical perspective, multi-center prospective external validations of promising metabolomic biomarker panels and machine learning (ML) models designed for delirium, EA, AKI, infection, and stress hyperglycemia, among others, is essential [20]. Such validation cohorts are necessary for evaluating the clinical performance and generalizability of these models and should be considered an essential prerequisite before using any metabolomics-based technology in routine clinical practice. In addition, interventional studies of personalized risk stratification and dosing algorithms derived from metabolomics against conventional management strategies will be needed.

From a translational perspective, the next step would involve continued development of rapid and inexpensive metabolomics analytical methods capable of supporting point-of-care testing [7]. The inclusion of metabolomics and multi-omics results into electronic health records-based decision-support systems should be informed by human factors research [21, 35].

Dedicated health economic evaluations should be conducted for the application of metabolomics within the perioperative pathway in high-risk populations, where the potential clinical and economic benefits may be greatest [33]. Finally, education and training of anesthesiologists, surgeons, laboratory scientists, and data scientists in metabolomics and multi-omics approaches will be essential for successful clinical implementation [36].

6. Conclusion

Perioperative metabolic phenotyping represents a promising approach in risk stratification and anesthesia dosing by integrating metabolomics, pharmacometabolomics, pharmacogenomics, and AI into the field of precision medicine. Several high-quality studies in the areas of anesthesia and surgery have demonstrated metabolite-based signatures associated with perioperative risk, organ dysfunction, and neurological function outcomes, providing biologically relevant information that may complement other clinical tools.

However, several important considerations remain. Heterogeneous methodologies, lack of external validation, the necessity of rigorous clinical trials, and uncertainties regarding cost-effectiveness must be addressed if perioperative metabolic phenotyping is to progress toward routine clinical use. If these challenges are successfully addressed, metabolic phenotyping has the potential to transform perioperative care by enabling a more biologically informed and patient-specific approach than is currently available.

AVAILABILITY OF DATA AND MATERIALS

Data sharing does not apply to this article, as no datasets were generated or analysed during the current study.

AUTHOR CONTRIBUTIONS

RY—conceptualization, methodology, literature search, data curation, formal analysis, manuscript drafting, critical revision, and final approval of the manuscript. DB—conceptualization, methodology, literature search, data interpretation, manuscript drafting, critical revision, supervision, and final approval of the manuscript. Both authors contributed equally to the intellectual content of the manuscript and approved the final version for publication.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

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

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