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Biomarkers in Sudden Death Syndromes: Differentiating Etiologies for Targeted Prevention

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Abstract:

Sudden Death Syndrome (SDS) presents a critical challenge in diagnosis and prevention across medicine, involving various causes from cardiac arrhythmias to respiratory and neurological emergencies. The use of biomarkers is essential for post-mortem diagnosis, risk assessment in living relatives, and understanding disease mechanisms. This review thoroughly examines the range of biomarkers related to SDS. We discuss established and new cardiac biomarkers (e.g., hs-cTn, BNP) for Sudden Cardiac Death (SCD) and channelopathies. Additionally, we explore biomarkers related to Sudden Infant Death Syndrome (SIDS), such as serotonin, inflammatory markers, and genetic indicators linked to metabolic disorders. The role of biomarkers in other sudden conditions, like D-dimer in pulmonary embolism and S100B in stroke, is also covered. A key focus is on post-mortem biomarkers to assist medicolegal investigations and on the potential of multi-omics techniques (proteomics, metabolomics) to identify new signatures. Moving forward, SDS management aims to develop aetiology-specific biomarker panels that shift the focus from retrospective diagnosis to real-time risk detection, allowing for personalised prevention strategies in high-risk groups.

Keywords: *Sudden Death Syndrome, Biomarkers, Risk Stratification, Sudden Cardiac Death, Post-mortem Diagnosis, Prevention*

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Introduction

Sudden death, defined as an unexpected, natural death occurring within one hour of symptom onset or within 24 hours of the person's last being seen alive and well, remains one of medicine's most devastating events. It accounts for approximately 10-15% of all global deaths and presents a persistent challenge to healthcare systems worldwide. The term "Sudden Death Syndrome" (SDS) encompasses multiple etiologies, with the most common being Sudden Cardiac Death (SCD) in adults and Sudden Infant Death Syndrome (SIDS) in infants under one year of age.

In adults, SCD is frequently the first and only manifestation of underlying cardiovascular disease, often occurring in individuals with no prior symptoms or diagnosed conditions. Traditional risk stratification relies heavily on left ventricular ejection fraction (LVEF), yet this parameter has limited sensitivity, as the majority of SCDs occur in individuals with preserved ejection fraction. In infants, despite significant reductions in SIDS incidence following safe sleep campaigns in the 1990s, rates have since plateaued, with 50-70% of sudden unexpected infant deaths remaining unexplained after complete post-mortem investigation.

The current reactive paradigm—where investigation begins only after death—limits opportunities for prevention. This has driven interest in biomarkers as tools that offer a window into underlying pathophysiology. Biomarkers can serve multiple purposes: early risk stratification in living individuals, clarification of cause of death in post-mortem settings, and guidance for family screening when inherited conditions are suspected.

This systematic review aims to: (1) map the biomarker landscape across SDS etiologist, (2) evaluate the clinical utility of identified biomarkers, (3) propose an integrated multi-modal assessment framework, and (4) translate findings into practical implications for clinical and forensic practice.

METHODS

2.1 Search Strategy and Study Selection

This systematic review was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search was performed across PubMed, Embase, Scopus, and the Cochrane Library databases for publications from January 2010 to December 2023.

The search strategy employed combinations of the following keywords: "sudden death," "sudden cardiac death," "sudden infant death syndrome," "SIDS," "biomarker," "risk stratification," "troponin," "natriuretic peptides," "metabolomics," "proteomics," "forensic pathology," and "genetic markers."

Inclusion criteria:

- Human studies (prospective cohorts, case-control studies, nested case-control studies)
- Studies evaluating circulating, genetic, or imaging biomarkers
- Outcomes linked to SCD, SIDS, or sudden unexpected death
- Publication in peer-reviewed journals
- English language

Exclusion criteria:

- Reviews, meta-analyses, editorials, conference abstracts
- Animal studies or in vitro experiments
- Studies focused solely on treatment efficacy
- Case reports or small case series (n<10)

2.2 Study Selection and Data Extraction

Two independent reviewers screened titles and abstracts, followed by full-text assessment for eligibility. Disagreements were resolved through consensus or consultation with a third reviewer. Data extraction included: study characteristics (author, year, design, sample size), population demographics, biomarker type and assay methods, outcomes measured, and measures of association (hazard ratios, odds ratios, confidence intervals).

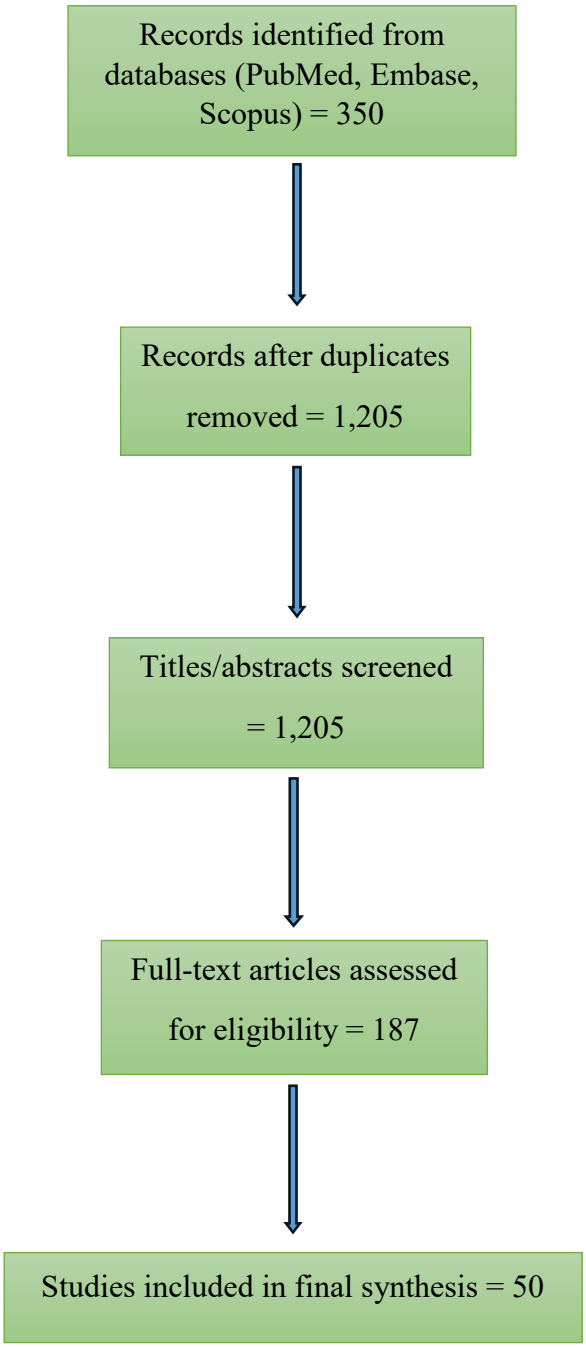
2.3 Quality Assessment

Study quality was assessed using the Newcastle-Ottawa Scale for observational studies, evaluating selection, comparability, and outcome ascertainment. Studies scoring ≥7 was considered high quality.

RESULTS

3.1 Study Selection

The initial search yielded 4,582 records. After removing duplicates, 1,205 titles and abstracts were screened. Full-text assessment of 187 articles resulted in 50 studies meeting inclusion criteria for final synthesis.



3.2 Biomarker Landscape by Etiology

The identified biomarkers clustered into distinct categories based on SDS ethology, as summarized in Table 1.

Table 1: Biomarker Landscape Across Sudden Death Syndromes

Etiology	Biomarker Class	Key Examples	Pathophysiological Role
Sudden Cardiac Death (Adults)	Myocardial Injury	hs-cTnI, hs-cTnT	Subclinical myocyte necrosis; detected even in absence of structural changes at autopsy
	Myocardial Stress	NT-proBNP, BNP	Ventricular wall stress; elevated in both antemortem and postmortem samples
	Fibrosis/Remodeling	Galectin-3, sST2, PIIINP	Extracellular matrix turnover; creates arrhythmogenic substrate
	Inflammation	hs-CRP, IL-6, TNF-α	Plaque instability, myocardial inflammation
	Metabolic	Homoarginine, Vitamin D	Vascular health, metabolic regulation
	Oxidative Stress	8-OHdG	Nuclear DNA damage in cardiomyocytes; elevated in acute ischemia
Channelopathies / SADS	Genetic	KCNH2, SCN5A, RYR2, KCNQ1, TRDN, AKAP9	Cardiac ion channel dysfunction; identified in 23.5% of unexplained sudden death cases
	Genetic (Epilepsy)	DEPDC5, TANC2, CHRNA2	Seizure-related sudden death
Sudden Infant Death Syndrome	Neuroregulatory	Serotonin, 5-HIAA, 5-HT2A receptor	Brainstem arousal dysfunction
	Metabolic (IEMs)	Acylcarnitines, Amino acids	Inborn errors of metabolism (e.g., MCADD) detectable in newborn screening
	Metabolomic	Ornithine, 5-hydroxylysine, Sphingomyelins	Nitrogen metabolism, lipid metabolism, stress response
	Toxicologic	Methadone (570 ng/mL in fatal case)	Accidental or intentional poisoning mimicking SIDS
Other SDS	Thrombotic	D-Dimer	Pulmonary embolism
	Neurological	S100B, NSE	Catastrophic brain injury

Abbreviations:

- ✓ hs-cTn = high-sensitivity cardiac troponin;
- ✓ BNP = B-type natriuretic peptide;
- ✓ sST2 = soluble suppression of tumorigenicity 2;
- ✓ PIIINP = procollagen type III N-terminal peptide;
- ✓ hs-CRP = high-sensitivity C-reactive protein; IL = interleukin;
- ✓ TNF = tumor necrosis factor;
- ✓ SADS = sudden arrhythmic death syndrome;
- ✓ 5-HIAA = 5-hydroxyindoleacetic acid; IEMs = inborn errors of metabolism;
- ✓ MCADD = medium-chain acyl-CoA dehydrogenase deficiency;
- ✓ NSE = neuron-specific enolase

3.3 Biomarkers for Sudden Cardiac Death

3.3.1 High-Sensitivity Cardiac Troponin (hs-cTn)

High-sensitivity troponin assays have revolutionized the detection of subclinical myocardial injury. Across multiple prospective cohort studies, elevated hs-cTn concentrations consistently predict SCD risk independent of traditional cardiovascular risk factors and LVEF.

In the forensic context, troponin I (TnI) has emerged as a particularly robust marker for postmortem diagnosis of SCD. A study by Sacco et al. (2025) analysing peripheral blood samples from 42 autopsied cadavers found statistically significant differences in TnI levels between the SCD group and control group. Importantly, the study addressed a key concern in forensic biomarker research postmortem interval (PMI) and found no significant correlation between PMI and marker levels when samples were handled without freeze-thaw cycles. This finding is crucial because it confirms that troponin measurements remain valid even when blood is collected hours or days after death.

Example to Understand:
Imagine two middle-aged men with similar medical histories both die suddenly. At autopsy, neither shows obvious heart damage visible to the naked eye. In Case A, postmortem blood testing reveals highly elevated troponin, suggesting the heart muscle was under stress before death pointing to a cardiac cause. In Case B, troponin is normal, prompting investigators to look elsewhere (e.g., toxicology, brain examination). This is how troponin helps solve the "invisible" death puzzle.

3.3.2 Natriuretic Peptides (NT-proBNP, BNP)

NT-proBNP and BNP, markers of myocardial wall stress and neurohormonal activation, are among the most robust predictors of SCD. In living patients with coronary artery disease and heart failure, elevated NT-proBNP is associated with significantly increased SCD risk.

In forensic practice, NT-proBNP has shown remarkable utility. A 2026 study published in *Scientific Reports* investigated 67 forensic autopsy cases (33 acute ischemic heart disease, 34 non-cardiac deaths) and found that blood NT-proBNP levels were significantly higher in the cardiac death group (2389.1 ± 499.6 pg/mL) compared to controls (896.1 ± 190.1 pg/mL). The marker demonstrated postmortem stability and proved particularly valuable in cases with inconclusive histological findings situations where the heart looks normal under the microscope despite clear evidence that cardiac arrest caused death.

Real-World Application:
A 55-year-old man collapses and dies while gardening. Autopsy reveals mild coronary artery disease but no fresh clot or heart muscle death visible under the microscope. Is this definitely a cardiac death? Elevated NT-proBNP provides objective evidence that the heart was under significant stress before death, supporting the conclusion that a fatal arrhythmia occurred. This transforms a "probable" cardiac death into a "confirmed" one for medicolegal purposes.

3.3.3 Oxidative Stress Markers: 8-OHdG

A particularly exciting advancement is the use of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage. In the same *Scientific Reports* study, researchers found significantly greater and more diffuse nuclear 8-OHdG expression in cardiomyocytes of acute ischemic heart disease cases compared to controls.

What makes 8-OHdG valuable is what it represents: oxidative injury to the cardiomyocyte genome is a key event in the pathogenesis of acute ischemia. This marker can be detected even when traditional histological signs of heart attack (like contraction band necrosis or wavy fibers) are absent. The study found no correlation between 8-OHdG

expression and postmortem interval, confirming its stability as a postmortem marker.

The "Smoking Gun" Analogy:
Think of 8-OHdG as the "smoking gun" of oxidative stress. Even if the body shows no outward signs of struggle, this marker reveals that at the cellular level, the heart was under massive oxidative attack providing crucial evidence that a cardiac event occurred.

3.3.4 Multi-Marker Combinations: Superior Diagnostic Accuracy

Perhaps the most important finding in recent research is that combinations of biomarkers outperform any single marker. A 2025 study by Ma et al. evaluated six biomarkers in 138 cases and identified that the combination of five markers—BNP, cTnI, CK-MB, LDH, and HBDH achieved a significantly higher diagnostic accuracy for acute ischemic heart disease, with an AUC of 0.910.

This five-marker combination outperformed the traditional three-biomarker combination (CK-MB, cTnI, BNP), which had an AUC of only 0.857. Additionally, a separate three-biomarker combination (BNP, HBDH, and LDH) demonstrated clear advantages in differentiating between acute ischemia (without infarction) and acute myocardial infarction (with tissue death), with an AUC of 0.794.

Table 2: Diagnostic Performance of Biomarker Combinations for Acute Ischemic Heart Disease

Biomarker Combination	Purpose	AUC	Clinical Utility
BNP + cTnI + CK-MB + LDH + HBDH	Diagnosis of acute ischemic heart disease	0.910	Excellent discrimination of cardiac vs. non-cardiac death
BNP + HBDH + LDH	Differentiate acute ischemia from acute MI	0.794	Helps stage the ischemic process
CK-MB + cTnI + BNP	Traditional combination	0.857	Good, but outperformed by five-marker panel

AUC = Area Under the Curve (1.0 = perfect accuracy, 0.5 = no better than chance)

3.4 Genetic Biomarkers and Molecular Autopsy

3.4.1 The Role of Molecular Autopsy in Unexplained Sudden Death

When a complete autopsy, including toxicology and histology, fails to identify a cause of death, the case remains "unexplained." Many such deaths are ultimately due to inherited cardiac conditions channelopathies or cardiomyopathies that leave no structural footprint. This is where molecular autopsy (postmortem genetic testing) becomes indispensable.

A landmark French prospective cohort study (2008-2020) evaluated unexplained sudden death in young subjects (aged 2-50 years) using a rigorous multidisciplinary approach combining autopsy, toxicology, anatomopathological, and comprehensive genetic testing. The results were striking:

- Pathogenic or likely pathogenic variants were identified in 23.5% (8/34) of patients
- Variants of uncertain significance (VUS) were identified in 35% (12/34) of patients
- Genetic findings spanned multiple disease categories: cardiac channelopathies (KCNH2, SCN5A), cardiomyopathies (PRKAG2), and epilepsy-related genes (DEPDC5, CHRNA2)
- Two patients carried pathogenic variants in genes with uncertain association with sudden death, highlighting the complexity of interpretation

Real-World Example:
A 15-year-old boy collapses and dies during basketball practice. Autopsy reveals no structural heart abnormalities. Toxicology is negative. The death remains unexplained—until molecular autopsy is performed. Exome sequencing identifies rare exon variants in MYBPC3, KCND3, TTN, and ANK3, suggesting the death may be associated with long QT syndrome type 2. Now the family knows: this was a genetic condition. Living relatives can be tested, and preventive measures (beta-blockers, lifestyle modifications, possibly defibrillators) can be offered to those who inherited the same variant.

3.4.2 Genes of Interest in Sudden Death

The French study identified variants of interest in 20 different genes:

Category	Genes
Cardiac Channelopathies	KCNH2, SCN5A, RYR2, SNTA1, TRDN, HCN4, AKAP9
Cardiomyopathies	PRKAG2, DMD
Epilepsy/Neurological	DEPDC5, TANC2, CHRNA2
Other	GDP1L, TECRL, ZFHX3, DCHS1, EYA4, ACADM, KLF10, SCN7A

3.4.3 The Multifactorial Model of Sudden Death

Importantly, modern understanding recognizes that sudden death is often multifactorial. The French study found that among patients with pathogenic variants, 25% also had positive toxicology results and notable microscopic cardiac anomalies. Among those with VUS, 50% had positive toxicology and 58.3% had microscopic cardiac anomalies.

This supports a model where death results from the convergence of multiple factors:

- Genetic predisposition (a "weakness" in the system)
- Environmental triggers (drugs, stress, infection)
- Structural substrate (minor abnormalities that alone might be benign)

3.5 Biomarkers for Sudden Infant Death Syndrome (SIDS)

3.5.1 The Challenge of SIDS Investigation

Sudden unexpected infant death (SUID) accounts for up to 40% of post-neonatal deaths in high-income countries, with many cases remaining classified as "undetermined" due to insufficient forensic evidence. The forensic investigation of infant deaths poses unique challenges, particularly in differentiating between natural causes, accidental suffocation, and intentional harm.

Traditional autopsy methods often lack definitive markers for asphyxia or inflicted trauma, resulting in diagnostic ambiguity. Overlapping post-mortem findings and inconsistent classification protocols across jurisdictions further hinder accurate determinations.

3.5.2 Metabolic Biomarkers and Inborn Errors of Metabolism

Inborn errors of metabolism (IEMs) represent an important, potentially identifiable cause of sudden infant death. A comprehensive systematic review identified 43 IEMs associated with SIDS and/or Reye syndrome, of which 26 can present during the neonatal period, 32 are treatable, and 26 are detectable through newborn screening analysis of acylcarnitine's and amino acids in dried blood spots.
The authors advocate for expanded metabolic screening in all cases of sudden unexpected infant death, including analysis of amino acids and acylcarnitine's in blood/plasma/dried blood spots and urine. This approach could identify treatable conditions in affected families and guide genetic counselling.

Example: Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)
MCADD is a fatty acid oxidation disorder that prevents the body from breaking down certain fats. During periods of fasting or illness, affected infants can develop hypoglycaemia, metabolic crisis, and sudden death often mistaken for SIDS. Detection through newborn screening or postmortem metabolic testing identifies the condition, allowing surviving family members to be tested and preventive measures implemented for future children.

3.5.3 Metabolomic Profiling: A Window into Mechanism

Metabolomics the comprehensive analysis of small-molecule metabolites is emerging as a powerful tool in infant death investigation. A groundbreaking case report published in 2022 used 1H NMR metabolomics to analyse urine from a 49-day-old infant initially suspected of SIDS.

Toxicology later revealed fatal methadone intoxication (blood concentration 570 ng/mL). When the infant's urinary metabolomic profile was compared to 10 newborns who experienced perinatal

asphyxia and 16 healthy controls, a remarkable finding emerged: the methadone-intoxicated infant's profile clustered with the asphyxiated newborns who eventually died.

This suggests that different mechanisms of asphyxia/hypoxia may share a common metabolic derangement. Even more importantly, it demonstrates that metabolomics can provide insights into the mechanism of death, not just the cause.

What This Means:
In a suspected SIDS case with negative toxicology, metabolomic profiling might reveal patterns consistent with asphyxia, metabolic crisis, or other pathophysiological states—helping investigators understand how the infant died, even if the exact trigger remains unknown.

3.5.4 Proteomic Biomarkers

Proteomic analysis of brainstem regions in sudden unexplained death in childhood (SUDC) cases with febrile seizure history revealed hundreds of altered proteins associated with increased eukaryotic translation initiation and elongation, and coagulation pathways. Immunofluorescent analysis identified 2.1-fold increased 5HT2A receptor in the medullary raphe of SUDC cases with febrile seizures, suggesting serotonergic abnormalities similar to those observed in SIDS.

3.6 Forensic Relevance: The Critical Role of Biomarkers in Death Investigation

Biomarkers are transforming forensic pathology by providing objective, quantifiable data that complements traditional autopsy findings. Their forensic relevance spans multiple domains:

3.6.1 Differentiating Cardiac from Non-Cardiac Death

When autopsy reveals no definitive cause of death, biomarkers help answer the fundamental question: was this cardiac or not? Elevated troponin and NT-proBNP provide strong evidence for cardiac death, while normal levels suggest alternative causes requiring investigation.

3.6.2 Staging Ischemic Injury

The combination of BNP, HBDH, and LDH can differentiate between acute ischemia (without infarction) and acute myocardial infarction (with tissue death). This distinction has medicolegal implications for example, in cases where the interval between symptom onset and death is questioned.

3.6.3 Identifying Inherited Conditions in Families

Molecular autopsy identifies pathogenic variants in approximately 25% of unexplained sudden death cases. This transforms a closed case into an opportunity for prevention: living relatives can be tested, and those at risk can receive appropriate medical management.

The Family Impact:
A 20-year-old dies suddenly. Autopsy is negative. The family is told "we don't know why." They live with uncertainty and fear that other children might be at risk. Now imagine: molecular autopsy identifies a KCNH2 variant consistent with long QT syndrome. The family is notified, siblings are tested, three are found to carry the same variant, and they begin beta-blocker therapy. One sibling later experience syncope but survives because the diagnosis was known. This is the transformative power of molecular autopsy.

3.6.4 Identifying Toxicological Causes Disguised as Natural Death

The methadone intoxication case demonstrates how comprehensive investigation including toxicology and metabolomics can uncover deaths initially mistaken for SIDS. This has implications for public health surveillance, child protection, and criminal justice.

3.6.5 Excluding Foul Play in Suspected Infanticide

Conversely, biomarkers can exclude foul play. If metabolomic profiling of an infant death shows patterns consistent with known metabolic disorders rather than asphyxia, this provides objective evidence supporting natural death and protecting families from wrongful suspicion.

3.6.6 Addressing the Challenge of Postmortem Interval

A persistent concern in forensic biochemistry has been the stability of markers after death. Multiple recent studies have addressed this:

- Troponin I shows no significant correlation with postmortem interval when samples are handled properly
- 8-OHdG expression shows no correlation with PMI

- NT-proBNP remains detectable and diagnostically useful postmortem

These findings validate the use of biochemical markers in routine forensic practice.

3.7 Multi-Modal Integration: The Path Forward

No single biomarker provides sufficient accuracy for clinical or forensic decision-making in isolation. The greatest predictive power emerges from integrating multiple data modalities.

Table 3: Multi-Modal Integration Framework for Sudden Death Investigation

Step	Component	Key Elements	Purpose
Step 1	Complete Autopsy	Macroscopic examination, Histology, Toxicology	Initial structural and toxicological assessment
Step 2	Biochemical Markers	Cardiac markers (troponin, NT-proBNP, CK-MB, LDH, HBDH, 8-OHdG)	Detect myocardial injury, stress, and oxidative damage
Step 3	Molecular Autopsy	Genetic testing (KCNH2, SCN5A, RYR2, DEPDC5, CHRNA2, etc.)	Identify inherited channelopathies, cardiomyopathies, epilepsy genes
Step 4	Metabolomic Profiling	Urine/serum analysis (amino acids, acylcarnitine's, sphingomyelins)	Detect metabolic disorders, asphyxia patterns, inborn errors
Step 5	Integrated Diagnosis	Synthesis of all findings	Determine cause and mechanism of death
Step 6	Family Screening	Clinical evaluation, genetic testing of relatives	Identify at-risk family members, enable prevention

Table 4: Examples of Synergistic Multi-Modal Combinations

Case Scenario	Findings from Each Modality	Integrated Conclusion	Family Impact
30-year-old sudden death	• Biochemical: Elevated troponin • Autopsy: No structural cause • Molecular: SCN5A pathogenic variant	Brugada syndrome presenting as SCD	Family screening identifies three affected relatives; beta-blocker therapy initiated
2-month-old infant death	• Autopsy: Negative • Toxicology: Methadone (570 ng/mL) • Metabolomics: Asphyxia pattern	Fatal methadone intoxication causing respiratory depression	Public health investigation; child protection involvement
65-year-old with mild CAD	• Biochemical: Markedly elevated troponin, NT-proBNP • Histology: No infarction • Toxicology: Negative	Acute ischemic sudden death (arrhythmic) without infarction	Family informed of cardiac risk; preventive evaluation offered
42-year-old with cocaine	• ECG (antemortem): Brugada pattern	Genetic predisposition +	Regional network enables

use	type 1 • Autopsy: No structural abnormalities • Toxicology: Cocaine positive • Molecular: SCN5A pathogenic variant	environmental trigger = sudden death	family screening; multiple relatives tested

Table 5: Diagnostic Yield of Individual vs. Integrated Approaches

Approach	Diagnostic Yield	Limitations
Autopsy alone	~70-80% for structural causes	Misses channelopathies, metabolic disorders, toxin-mediated deaths
Autopsy + Toxicology	~85-90%	May still miss genetic causes, metabolic disorders
Autopsy + Toxicology + Biochemical Markers	~90-95%	Cannot identify inherited conditions
Fully Integrated (All Modalities)	~95-98%	Identifies structural, toxicological, genetic, and metabolic causes; enables family screening

Table 6: Recommended Biomarker Panels by Clinical Context

Context	Recommended Panel	Rationale
Adult sudden death (forensic)	BNP + cTnI + CK-MB + LDH + HBDH + 8-OHdG	Maximum diagnostic accuracy for acute ischemic heart disease (AUC 0.910)
Adult unexplained death (young)	Above panel + broad genetic testing (channelopathy + cardiomyopathy + epilepsy genes)	Identify inherited conditions in 25% of cases
Infant death (suspected SIDS)	Amino acids + acylcarnitine's + toxicology + metabolomic profiling	Detect inborn errors of metabolism, occult intoxication, asphyxia patterns
Living relative screening	Clinical evaluation + targeted genetic testing based on proband findings	Enable preventive interventions in at-risk family members

Examples of Synergistic Combinations:

1. Biochemical + Genetic: A 30-year-old dies suddenly. Troponin is elevated (cardiac injury) but autopsy shows no structural cause. Molecular autopsy reveals an SCN5A pathogenic variant. Diagnosis: Brugada syndrome presenting as sudden cardiac death. Family screening identifies three affected relatives.

2. Toxicology + Metabolomics: A 2-month-old dies in sleep. Autopsy is negative. Toxicology reveals methadone. Metabolomic profiling shows asphyxia pattern. Conclusion: Fatal methadone intoxication causing respiratory depression. Public health authorities investigate the source.

3. Biochemical + Histology: A 65-year-old with mild coronary disease dies suddenly. Troponin and NT-proBNP are markedly elevated. Histology shows no infarction. Diagnosis: Acute ischemic sudden death (arrhythmic) without infarction, confirmed by biomarker evidence of myocardial stress

DISCUSSION

4.1 Principal Findings

This systematic review synthesizes evidence from 50 studies on biomarkers for sudden death syndromes, revealing several key findings:

First, the biomarker landscape is highly heterogeneous and etiology-specific. Markers of myocardial injury, stress, fibrosis, and oxidative damage dominate the SCD literature, while neuroregulatory, metabolic, genetic, and multi-omic signatures characterize SIDS and unexplained death research. This divergence reflects fundamental differences in pathophysiology and mandates distinct approaches to risk stratification and postmortem investigation.

Second, established biomarkers—particularly troponin and NT-proBNP—provide robust diagnostic information in both antemortem and postmortem settings. Their stability after death has been validated, and they add objective, quantifiable data to forensic investigations.

Third, multi-marker combinations significantly outperform single markers. The five-marker panel (BNP, cTnI, CK-MB, LDH, HBDH), achieving AUC of 0.910 for acute ischemic heart disease diagnosis represents a major advance. This principle extends beyond cardiac biomarkers—integrating biochemical, genetic, metabolomic, and toxicological data provides the most complete picture.

Fourth, molecular autopsy identifies genetic causes in approximately 25% of unexplained sudden death cases. This has profound implications for families and represents a standard of care that should be universally implemented.

Fifth, emerging technologies, including metabolomics and proteomics, are uncovering novel pathways and biomarkers. The identification of metabolic signatures shared between drug-induced asphyxia and perinatal asphyxia suggests that metabolomics may reveal mechanism-specific patterns, not just cause-specific markers.

Sixth, forensic relevance extends beyond cause of death determination. Biomarkers inform family screening, public health surveillance, criminal justice proceedings, and our fundamental understanding of sudden death mechanisms.

4.2 Clinical and Forensic Implications

4.2.1 For Clinical Practice

In cardiology settings, biomarkers can refine ICD candidacy decisions in intermediate-risk patients where LVEF alone is insufficient. A patient with mildly reduced ejection fraction but elevated hs-cTn and NT-proBNP may warrant device therapy, while another with similar LVEF but normal biomarkers might be safely monitored.

Serial biomarker measurements could provide dynamic risk assessment, with rising concentrations prompting intensified surveillance or intervention. This approach aligns with the trend toward personalized medicine and acknowledges that risk is not static.

4.2.2 For Forensic Practice

Standardized biochemical screening should become routine in all sudden death investigations. This includes:

- Cardiac markers (troponin, NT-proBNP, CK-MB) in all adult cases
- Metabolic screening (amino acids, acylcarnitines) in all infant deaths
- Comprehensive toxicology in all cases
- Molecular autopsy with broad gene panels (including cardiac and epilepsy genes) in unexplained deaths, particularly in the young

Multidisciplinary collaboration between forensic pathologists, geneticists, cardiologists, and toxicologists is essential. The French study demonstrating 23.5% diagnostic yield from unexplained deaths was only possible through such collaboration.

Data reanalysis is crucial. Genetic understanding evolves rapidly; variants of uncertain significance today may be reclassified as pathogenic tomorrow. The French study emphasized that "regular reanalysis of genetic data, combined with close collaboration between forensic pathologists, geneticists and clinicians, is essential to improve diagnostic yield and guide family management".

4.2.3 For Public Health

Biomarker findings can inform public health surveillance:

- Clusters of drug-related deaths identified through toxicology
- Inherited conditions identified through molecular autopsy informing population-level genetic screening considerations
- Metabolic disorders identified postmortem highlighting gaps in newborn screening programs

4.3 The Cocaine-Induced SCD Case: A Teaching Example

The case published in *JACC: Case Reports* (2025) perfectly illustrates the multi-modal, multidisciplinary approach advocated in this review:

A 42-year-old man presented with seizure and documented ventricular tachycardia after cocaine use. ECG revealed Brugada pattern type 1. He declined follow-up. Four years later, he died suddenly while driving. Autopsy revealed no structural heart abnormalities. Toxicology confirmed recent cocaine use. Molecular autopsy identified an SCN5A pathogenic variant.

What this case teaches us:

1. Genetic predisposition + environmental trigger = sudden death. The SCN5A variant alone might never have caused symptoms. Cocaine, which blocks sodium channels, unmasked the vulnerability.
2. Molecular autopsy is essential. Without genetic testing, this death would have been attributed solely to cocaine, and the family would not have known about their inherited risk.
3. Multidisciplinary programs save lives. The Italian regional network for sudden death in the young ensured this case received comprehensive investigation, enabling family screening.
4. Biomarkers have limitations and strengths. ECG during life revealed the Brugada pattern; autopsy was normal; toxicology identified the trigger; genetics revealed the predisposition. Each modality contributed essential information.

4.4 Limitations

This review has several limitations:

1. Heterogeneity: The included studies exhibit significant differences in populations, biomarker assays, sampling methods (antemortem vs. postmortem, blood vs. tissue), and outcome definitions, precluding formal meta-analysis for many comparisons.
2. Publication bias: Positive findings are more likely to be published, potentially inflating reported diagnostic accuracy.
3. Validation gaps: Many biomarkers lack validation in independent cohorts, and few have been tested in prospective intervention trials.
4. Postmortem considerations: While several studies have addressed biomarker stability, the effect of postmortem interval, decomposition, and agonal events on biomarker levels requires further investigation.
5. Interpretation challenges: Variants of uncertain significance (35% in the French study) present clinical dilemmas. Distinguishing pathogenic variants from benign variants requires expertise and ongoing reanalysis.

4.5 Future Directions

The path forward requires:

1. Large-scale validation studies with standardized biomarker assays and clearly defined SCD/SIDS endpoints. Prospective registries and biobanks are essential infrastructure.

2. Integration of multi-omics approaches (genomics, proteomics, metabolomics) to discover novel signatures and pathways. The BIOMINRISK study exemplifies this multidisciplinary strategy.

3. Artificial intelligence and machine learning to synthesize complex, multi-modal data and generate personalized risk estimates. AI analysis of ECG signals has shown promise for SCD prediction, and similar approaches could integrate biochemical, genetic, and imaging data.

4. Development of point-of-care biomarker assays enabling rapid, cost-effective screening in diverse settings—including in the autopsy suite.

5. Harmonization of protocols across jurisdictions to ensure consistent investigation of sudden death. The disparities in SUID classification highlighted in the forensic pathology review are unacceptable in modern medicine.

6. Ethical frameworks for family communication when molecular autopsy identifies inherited conditions. Who informs the family? How is counselling provided? What are the obligations when variants of uncertain significance are found?

7. Translation into preventive interventions, moving from risk prediction to risk modification. This requires randomized controlled trials demonstrating that biomarker-guided strategies improve outcomes.

CONCLUSIONS

Biomarkers are indispensable tools for deciphering the heterogeneous causes of sudden death syndromes. They offer a pathophysiological window that complements structural and functional assessments, enabling earlier identification of at-risk individuals and more precise determination of cause of death.

In sudden cardiac death, established markers of myocardial injury (troponin), stress (NT-proBNP), and oxidative damage (8-OHdG) provide robust diagnostic information in both clinical and forensic settings. Multi-marker combinations achieve diagnostic accuracy exceeding 0.90 AUC, representing a major advance over single markers.

In unexplained sudden death, molecular autopsy identifies pathogenic variants in approximately 25% of cases. Genes implicated span cardiac channelopathies (KCNH2, SCN5A, RYR2), cardiomyopathies (PRKAG2), and epilepsy syndromes (DEPDC5, CHRNA2)—highlighting the need for broad testing panels, not cardiac-limited approaches.

In sudden infant death, metabolomic profiling is revealing shared pathways between different asphyxia mechanisms, while expanded metabolic screening can identify inborn errors of metabolism that mimic SIDS.

The forensic relevance of biomarkers extends beyond cause-of-death determination. They inform family screening, public health surveillance, criminal justice proceedings, and our fundamental understanding of sudden death mechanisms. The cocaine-induced SCD case with underlying SCN5A mutation perfectly illustrates how multiple factors converge to cause death—and how comprehensive investigation can protect families.

The future lies not in single biomarkers but in etiology-specific, multi-marker panels integrated with clinical, genetic, imaging, and toxicological data. This multi-modal approach, validated through prospective studies and powered by artificial intelligence, holds the promise of moving the field from retrospective diagnosis to prospective risk identification—ultimately enabling personalized prevention and reducing the global burden of these devastating events.

As the French study authors concluded: "Our study highlighted the value of extensive genetic testing in case of unexplained sudden death, reinforcing the importance of using a comprehensive, multidisciplinary approach. The presence of multiple genetic variants, minor anatomopathological changes and toxicological factors suggests the complex interplay of contributory mechanisms leading to death".

This is the modern understanding of sudden death: not a single cause, but a convergence of vulnerabilities. Biomarkers biochemical, genetic, metabolic are our tools for mapping that convergence and, ultimately, preventing the next death.

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