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SYSTEMATIC REVIEW

Emergency Medical Services

# Intra-arrest blood-based biomarkers for out-of-hospital cardiac arrest: A scoping review

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## Abstract

**Objective:** Blood-based biomarkers play a central role in the diagnosis and treatment of critically ill patients, yet none are routinely measured during the intra-arrest phase of out-of-hospital cardiac arrest (OHCA). Our objective was to describe methodological aspects, sources of evidence, and gaps in research surrounding intra-arrest blood-based biomarkers for OHCA.

**Methods:** We used scoping review methodology to summarize existing literature. The protocol was designed a priori following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews. Inclusion criteria were peer-reviewed scientific studies on OHCA patients with at least one blood draw intra-arrest. We excluded in-hospital cardiac arrest and animal studies. There were no language, date, or study design exclusions. We conducted an electronic literature search using PubMed and Embase and hand-searched secondary literature. Data charting/synthesis were performed in duplicate using standardized data extraction templates.

**Results:** The search strategy identified 11,834 records, with 118 studies evaluating 105 blood-based biomarkers included. Only eight studies (7%) had complete reporting. The median number of studies per biomarker was 2 (interquartile range 1–4). Most studies were conducted in Asia (63 studies, 53%). Only 22 studies (19%) had blood samples collected in the prehospital setting, and only six studies (5%) had samples collected by paramedics. Pediatric patients were included in only three studies (3%). Out of eight predefined biomarker categories of use, only two were routinely assessed: prognostic (97/105, 92%) and diagnostic (61/105, 58%).

**Conclusions:** Despite a large body of literature on intra-arrest blood-based biomarkers for OHCA, gaps in methodology and knowledge are widespread.

KEYWORDS

advanced cardiac life support, biomarkers, cardiac arrest, emergency medical services, hematologic tests, out-of-hospital, prehospital, pulseless electrical activity, scoping review

# 1 | INTRODUCTION

## 1.1 | Background

Advanced cardiovascular life support for out-of-hospital cardiac arrest (OHCA) contains only a single branch point in its algorithm, which is based on the electrical activity of the heart.[1–3] No other physiologic biomarkers are algorithmically defined during the intra-arrest phase of OHCA resuscitations. Although clinical providers taught the "5 H's and 5 T's," a differential diagnosis for OHCA, there is no standardization on how to test or when to treat these, and other, potential underlying etiologies. Therefore, intra-arrest interventions for OHCA are frequently given empirically, without guidance from patient-specific data. As a result, few efficacious intra-arrest interventions exist. In the case of pulseless electrical activity (PEA), the treatment algorithm has been reduced to a single medication, epinephrine, and even its utility has been called into question by recent clinical trials.[4]

## 1.2 | Importance

Blood-based biomarkers play a central role in the diagnosis and treatment of essentially all critically ill patients. However, for OHCA, this often does not occur until after return of spontaneous circulation (ROSC). The principal reason why intra-arrest blood-based biomarkers are not routinely measured is operational: rapid on-scene treatment is preferred since OHCA is a highly time-dependent disease process and measuring blood-based biomarkers outside the hospital setting is challenging.[5] Although post-ROSC blood-based biomarkers are important for the clinical management of post-cardiac arrest syndrome, they are unlikely to inform intra-arrest management, given the dramatic pathophysiologic changes that occur when native heart function is restored.[6] Animal models, while critically important for studying the mechanics of cardiopulmonary resuscitation and developing hypotheses, cannot directly inform the pathophysiology of a human patient. For example, animal models of PEA frequently rely on asphyxia or countershocks to induce PEA, but up to 50% of PEA in humans is thought to have a non-electrical cardiac etiology, with increasing incidence of PEA perhaps driven by the rise in beta-blocker usage.[7]

## 1.3 | Goals

The goal of this investigation was to describe the key concepts, methodological aspects, sources of evidence, and gaps in the research surrounding intra-arrest blood-based biomarkers for OHCA to guide future research efforts. To achieve this, we used scoping review methodology.[8] In North America, intra-arrest medical care is often provided by paramedics in the prehospital setting, so this was a specific area of interest.

# 2 | METHODS

## 2.1 | Protocol and eligibility criteria

The study protocol was designed a priori following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews.[8] The protocol is described in total in this manuscript as per the International Prospective Register of Systematic Reviews (PROSPERO).[9] All data were publicly available, so the study was exempt from Institutional Review Board approval.

The inclusion criteria were: (1) primary peer-reviewed scientific manuscript/abstract, (2) OHCA, (3) human patients, and (4) at least one blood sample drawn intra-arrest. The exclusion criteria were: (1) secondary or non-peer-reviewed manuscript/abstract, (2) in-hospital cardiac arrest, (3) animal/laboratory studies, or (4) no blood drawn before ROSC or extracorporeal cardiopulmonary resuscitation (ECPR). In-hospital cardiac arrests are defined as those initially treated by hospital-based medical teams, while OHCA are defined as those initially treated by lay bystanders and/or 9-1-1 responders. In-hospital cardiac arrest was excluded since the underlying pathophysiology often differs from OHCA. Blood draws could occur in any setting, including in the hospital, so long as the patient met the definition of OHCA. We required studies to be peer-reviewed to ensure a minimum level of quality. We applied no language limitations, date restrictions, or exclusions based on study design.

## 2.2 | Information sources, search strategy, and selection process

A research librarian assisted in conducting an electronic literature search by using the databases PubMed (www.pubmed.ncbi.nlm.nih.gov) and Embase (www.embase.com). We also searched the reference sections from multiple versions of the American Heart Association's *Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care*, textbooks on cardiac arrest, and relevant review articles found by the search strategy. Finally, we asked experts in the field to provide any additional studies.

We used Medical Subject Headings terms for PubMed and Emtree Subject Headings for Embase to ensure that synonyms and associated terms were included in the search. Multiple searches were conducted in both databases, with each individual search using at least one heading for the broad category of cardiac arrest, and a second heading for the broad category of blood-based biomarker, combined with the Boolean Operator "AND." The following headings were used for PubMed: "out-of-hospital cardiac arrest," "heart arrest," "emergency medical services," "hospital emergency service," "metabolism," "electrolytes," "biomarkers," "metabolomics," "transcriptome," "troponin," "d-dimer," "blood proteins," "hormones," "drug overdose," and "hematologic tests." The following headings were used for Embase: "out of hospital cardiac arrest," "heart arrest," "emergency health service," "emergency ward," "metabolic disorder," "electrolyte," "medical

parameters," "metabolomics," "transcriptome," "troponin," "d-dimer test," "plasma protein," "hormones and agents acting on the endocrine system," "drug overdose," and "blood examination."

Two authors independently reviewed all titles from this search strategy for relevance based on the inclusion and exclusion criteria. If appropriate, the entire manuscript was then reviewed. A consensus of the authors was used to determine the final list of articles that met all criteria. The literature search was current as of December 15, 2022.

### 2.3 | Data charting and synthesis

Two authors performed data charting and synthesis in duplicate using a standardized data extraction template developed for this scoping review after the initial search, as described below. A consensus of the authors was used to resolve any inconsistencies and disagreements. We charted the following data for each study:

- Last name of first author
- Year of publication
- Geographic region of subject enrollment
- Age category of subjects (pediatrics defined as <15 years old)
- Subtype(s) of cardiac arrest investigated
- Setting(s) where blood draw(s) occurred
- Clinician(s) performing the blood draw(s)
- Stage(s) of resuscitation when blood draw(s) occurred (defined below)
- Whether serial blood samples were obtained
- Blood-based biomarker investigated
- Source(s) of blood
- Additive(s) in blood collection tube
- Whether laboratory methods for biomarker detection were described
- Time interval between blood collection and final processing (prehospital studies only)

The stages of resuscitation when blood draws could occur were categorized as follows. Few studies reported a per-minute accounting of blood draws, so a 5-min threshold was used only as a theoretical framework to align study investigators.

- Intra-arrest: while patient is pulseless
- At ROSC: <5 min after ROSC
- Post-ROSC: >5 min after ROSC
- At termination of resuscitation (ToR): <5 min before or after ToR
- At ECPR: <5 min after starting ECPR
- Post-ECPR: >5 min after starting ECPR

For each blood-based biomarker, we synthesized the following elements:

- Biomarker name
- Biologic function and/or plausibility as biomarker
- Number of studies investigating the biomarker
- Category of use for the biomarker (defined below)
- Qualitative summary of results (defined below)

We used the Biomarkers, Endpoints, and other Tools (BEST) Resource from the US Food and Drug Administration-National Institutes of Health (FDA-NIH) Biomarker Working Group to describe biomarker categories of use:[10]

- Diagnostic: presence of disease or subtype
- Monitoring: draw repeatedly to assess disease status
- Response: demonstrate biologic response to medical intervention
- Predictive: predict favorable or unfavorable effect from medical intervention
- Prognostic: predict likelihood of clinical outcome
- Safety: adverse event after medical intervention
- Surrogate endpoint: predicts a specific clinical benefit
- Susceptibility: potential for developing a disease not currently present

We counted the number of studies and biomarkers that fit into predefined categories. The overall goal of a scoping review is to identify key concepts and gaps in research, so a quantitative critical appraisal of individual studies and/or statistical combination of multiple studies is out of scope. A qualitative summary of results for each biomarker was undertaken to provide the reader with a general understanding of the available research, but this should not be considered a definitive assessment of biomarker utility. We used the following generalizations in these qualitative summaries:

- Associated: available studies have generally demonstrated associations (unadjusted and/or adjusted analyses)
- No association: available studies have generally not demonstrated any associations
- Uncertain association: available studies have produced conflicting results
- Short-term patient outcomes: ROSC, survival to hospital admission, or similar
- Long-term patient outcome: survival to hospital discharge, cerebral performance category score, or similar

Only published data were reported, and missing data were reported as such. Due to the large volume of missing data and the number of years since publication, contacting individual study investigators for additional data was not feasible. Studies that had incomplete reporting to fully assess all inclusion and exclusion criteria were reported as such.

## 3 | RESULTS

The search strategy identified a total of 11,834 records, of which 6914 were non-duplicates. After applying all inclusion and exclusion criteria, 118 studies were included in the scoping review, as shown in Figure 1.[11–128]

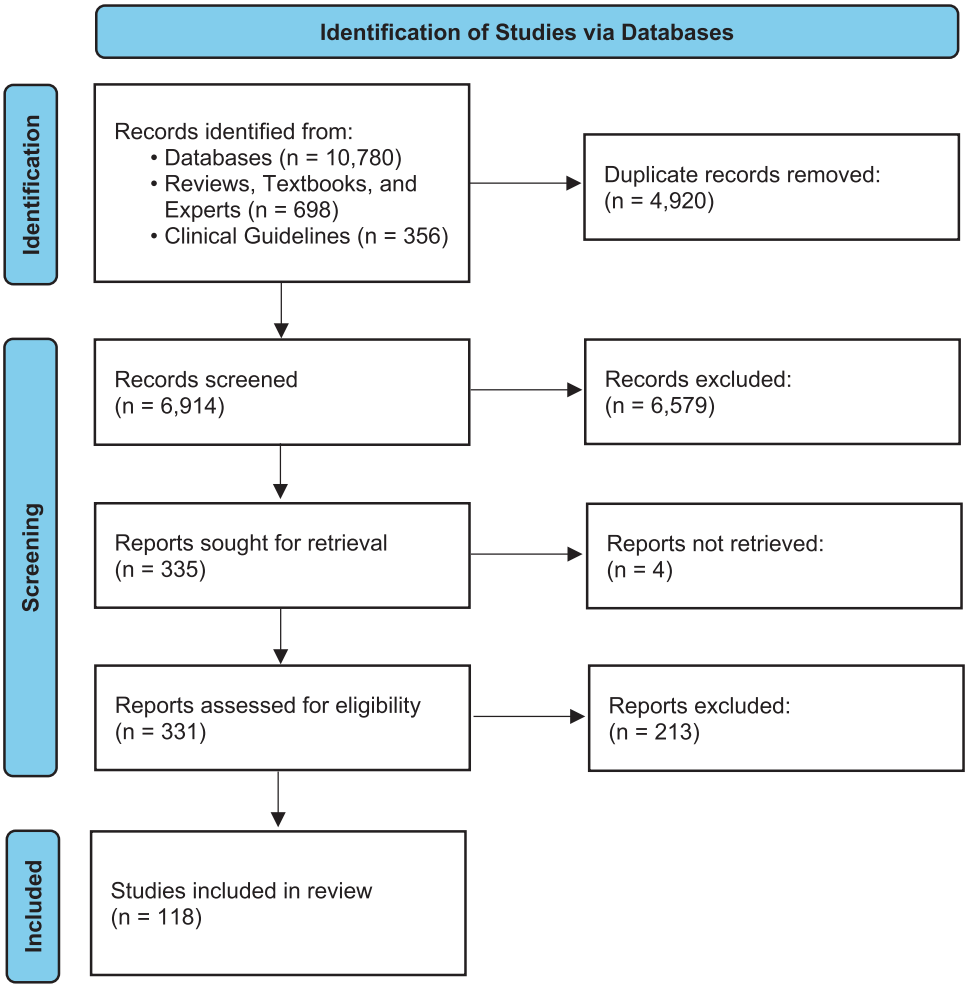


**FIGURE 1** Flow diagram of study selection.

These studies are described in detail in Tables 1–6. Incomplete reporting was common, especially for the stage of resuscitation when the blood draw occurred (eg, intra-arrest, post-ROSC). Due to these missing data, we could not fully assess the inclusion and exclusion criteria for 31 studies, but they were included in the scoping review to provide a broader overview of the state of the science. Only eight studies (7%) had complete reporting with no missing data.

The studies evaluated a total of 105 blood-based biomarkers. The median number of studies per blood-based biomarker was 2, with an interquartile range of 1–4. Qualitative summaries for each biomarker are provided in Table S1.

Synthesis of the 118 studies is provided in Table 7. Most of the studies were conducted in Asia (63 studies, 53%). Only 22 studies (19%) had blood samples collected in the prehospital setting, and only six studies (5%) had intra-arrest blood samples collected by paramedics in the prehospital setting.[12–14,20,82,83] Only three studies (3%) enrolled any pediatric patients.[24,90,114] Out of the eight categories of use for biomarkers defined by the BEST Resource, only two were routinely assessed: prognostic (97 out of 105 biomarkers, 92%) and diagnostic (61 out of 105 biomarkers, 58%).[10] The "predictive" category was assessed for only one biomarker, while the "susceptibility," "safety," and "surrogate endpoint" categories were never assessed in the field of resuscitation science.

## 4 | LIMITATIONS

The work described here, and scoping review methodology in general, has the following limitations. No specific clinical questions were asked, and a quantitative critical appraisal of study quality was not indicated, so results are not directly applicable to clinical medicine. Missing data may have affected results, and the likelihood of publication bias could not be assessed. Finally, novel blood-based biomarkers, especially those that have been investigated in animal studies but not human studies, are absent from this review.

## 5 | DISCUSSION

This scoping review encompasses over 45 years of resuscitation science on intra-arrest blood-based biomarkers for OHCA. Despite this large volume of research, heterogeneity of study design and gaps in

**TABLE 1** Blood gas and energy studies.

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Abramson et al. 2022[14] | Americas | Retrospective cohort | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: paramedic | Stage: intra-arrest<br>Serial: no | Glucose | Source: Ø<br>Tube: Ø | Ø<br>Time: 1 min |
| Ahn et al. 2018[16] | Asia | Interventional | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: yes | Bicarb | Source: arterial<br>Tube: Ø | Described |
| Bartos et al. 2020[19] | Americas | Retrospective cohort | Age: adult<br>Subtype: VF | Setting: hospital<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pO_2$, $pCO_2$, lactate | Source: arterial<br>Tube: Ø | Ø |
| Bender et al. 2007[20] | Europe | Interventional | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: physician, paramedic | Stage: intra-arrest, post-ROSC<br>Serial: yes | pH, $pO_2$, Bicarb, BE, Na, K, Hg | Source: venous, arterial<br>Tube: Ø | Ø<br>Time: Ø |
| Bishop and Weisfeldt 1976[21] | Americas | Prospective cohort | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: yes | pH, $pO_2$, Na, K, osmolality | Source: arterial<br>Tube: Ø | Ø |
| Brugger et al. 2019[24] | Europe | Retrospective cohort | Age: adult, peds<br>Subtype: cold | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, K | Source: Ø<br>Tube: Ø | Ø |
| Calbay et al. 2019[26] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest, at ROSC<br>Serial: yes | pH, $pO_2$, $pCO_2$, BE, lactate | Source: arterial<br>Tube: heparin | Described |
| Cannon et al. 1987[27] | Americas | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pO_2$, $pCO_2$, Na, K, Cl, $CO_2$, glucose, Mag | Source: arterial, venous<br>Tube: Ø | Described |
| Chen et al. 2011[28] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, Bicarb, glucose, WBC, Hct, Cr, Na, K, AST, CK-MB, troponin-I | Source: Ø<br>Tube: Ø | Ø |
| Chien et al. 2010[29] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, $pO_2$, Bicarb | Source: Ø<br>Tube: Ø | Described |
| Corral Torres et al. 2020[31] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: physician, nurse | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, Bicarb, BE, Na, K, Ca, lactate | Source: venous<br>Tube: Ø | Described<br>Time: 1 min |
| Dadeh and Nuanjaroan 2018[32] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Lactate | Source: Ø<br>Tube: Ø | Ø |
| Daou et al. 2020[33a] | Australia | Retrospective cohort | Age: adult<br>Subtype: ECPR | Setting: hospital<br>Clinician: Ø | Stage: intra-arrest, at ECPR<br>Serial: no | pH, AST, Cr, lactate | Source: Ø<br>Tube: Ø | Ø |
| Dorph et al. 2004[34] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | $pCO_2$ | Source: arterial<br>Tube: Ø | Described |

(Continues)

**TABLE 1** (Continued)

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Gando et al. 1997[38] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest, at ToR, post-ROSC<br>Serial: yes | pH, Bicarb, lactate, pyruvate, ionized Ca, total Ca | Source: arterial<br>Tube: heparin, perchloric acid | Described |
| Gennis et al. 1985[44] | Americas | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, bicarb | Source: arterial, venous<br>Tube: heparin | Described |
| Gruebl et al. 2021[45] | Europe | Retrospective cohort | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, K, lactate | Source: arterial, venous<br>Tube: Ø | Described<br>Time: 1 min |
| Hong et al. 2021[48] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: physician | Stage: intra-arrest<br>Serial: yes | pH, $pO_2$, $pCO_2$, Bicarb, lactate | Source: arterial<br>Tube: heparin | Described |
| Janata et al. 2003[52a] | Europe | Retrospective cohort | Age: adult<br>Subtype: PE | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | pH, lactate | Source: Ø<br>Tube: Ø | Ø |
| Jouffroy et al. 2014[54] | Europe | Retrospective cohort | Age: adult<br>Subtype: ECPR | Setting: hospital<br>Clinician: Ø | Stage: at ECPR, post-ECPR<br>Serial: yes | Lactate, BE | Source: arterial<br>Tube: Ø | Described |
| Kim et al. 2016[56] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pO_2$, $pCO_2$, Bicarb, BE, lactate, Na, K, glucose | Source: arterial<br>Tube: heparin | Described |
| Kurkciyan et al. 2000[62a] | Europe | Retrospective cohort | Age: Ø<br>Subtype: PE | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | pH, lactate | Source: Ø<br>Tube: Ø | Ø |
| Langhelle et al. 2000[64] | Europe | Interventional | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: physician | Stage: intra-arrest<br>Serial: yes | pH, $pCO_2$, $pO_2$, BE | Source: arterial<br>Tube: plain | Described<br>Time: 1 min |
| Lin et al. 2013[65] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pO_2$, $pCO_2$, Bicarb, BE, Na, K, glucose, Cr, AST, ALT, Hg, WBC, ammonia | Source: Ø<br>Tube: heparin | Described |
| Lin et al. 2018[67] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, K | Source: Ø<br>Tube: Ø | Ø |
| Lin et al. 2021[68] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH | Source: Ø<br>Tube: Ø | Ø |
| Linde et al. 2022[69] | Europe | Retrospective cohort | Age: adult<br>Subtype: ECPR | Setting: Ø<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pO_2$, $pCO_2$, BE, lactate, K | Source: Ø<br>Tube: Ø | Ø |
| Longstreth et al. 1986[72] | Americas | Prospective cohort | Age: Ø<br>Subtype: cardiac | Setting: prehospital<br>Clinician: Ø | Stage: intra-arrest, post-ROSC<br>Serial: yes | Glucose | Source: Ø<br>Tube: Ø | Ø<br>Time: Ø |
| Makino et al. 2005[74a] | Asia | Prospective cohort | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | pH, $pCO_2$, bicarb, BE, Na, K, Cl, ionized Ca, Mag, Phos, lactate, albumin | Source: arterial<br>Tube: heparin | Described |

(Continues)

**TABLE 1** (Continued)

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Masuda et al. 2003[75] | Asia | Prospective cohort | Age: adult<br>Subtype: witness | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, BE | Source: arterial, venous<br>Tube: heparin | Described |
| Matsuyama et al. 2020[77] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | $pCO_2$ | Source: Ø<br>Tube: Ø | Ø |
| Meislin 1980[78] | Americas | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: yes | pH, $pO_2$, $pCO_2$ | Source: arterial<br>Tube: Ø | Described |
| Morimura 2009[79] | Asia | Prospective cohort | Age: adult<br>Subtype: VF/pVT | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, $pO_2$, Bicarb | Source: arterial<br>Tube: Ø | Ø |
| Nehme et al. 2016[83] | Australia | Retrospective cohort | Age: adult<br>Subtype: cardiac | Setting: prehospital<br>Clinician: paramedic | Stage: intra-arrest<br>Serial: no | Glucose | Source: capillary<br>Tube: Ø | Described<br>Time: 1 min |
| Nelskyla et al. 2022[84] | Europe | Prospective cohort | Age: adult<br>Subtype: cardiac | Setting: prehospital<br>Clinician: physician | Stage: intra-arrest, at ROSC<br>Serial: yes | $pO_2$, $pCO_2$ | Source: arterial<br>Tube: heparin | Described<br>Time: 1 min |
| Nishioka et al. 2021[85] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Lactate | Source: Ø<br>Tube: Ø | Ø |
| Nowak et al. 1987[87] | Americas | Prospective cohort | Age: Ø<br>Subtype: cardiac | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$ | Source: arterial, venous<br>Tube: Ø | Ø |
| Okada et al. 2020[88] | Asia | Retrospective cohort | Age: adult<br>Subtype: ECPR | Setting: hospital<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH | Source: Ø<br>Tube: Ø | Ø |
| Okada et al. 2020[89a] | Asia | Retrospective cohort | Age: adult<br>Subtype: cold | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | pH, K, lactate | Source: Ø<br>Tube: Ø | Ø |
| Okada et al. 2021[90a] | Asia | Retrospective cohort | Age: peds<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | pH | Source: Ø<br>Tube: Ø | Ø |
| Ornato et al. 1985[91a] | Americas | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: physician | Stage: Ø<br>Serial: no | pH, $pO_2$, $pCO_2$ | Source: arterial<br>Tube: heparin | Ø |
| Prause et al. 2001[95] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: physician | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, $pO_2$, lactate, BE | Source: arterial<br>Tube: Ø | Described<br>Time: 2 min |
| Pytte et al. 2008[96] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: physician | Stage: at ToR<br>Serial: yes | pH, $pCO_2$, $pO_2$, BE | Source: arterial<br>Tube: Ø | Described<br>Time: 1 min |
| Rivers et al. 1992[97] | Americas | Prospective cohort | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest, at ROSC<br>Serial: yes | pH, $pO_2$, $pCO_2$, Bicarb, Hg | Source: arterial, venous<br>Tube: Ø | Described |
| Sariaydin et al. 2017[98] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, Bicarb, lactate, glucose, Hg, Cr, WBC, Na, K | Source: venous<br>Tube: heparin | Described |

(Continues)

**TABLE 1** (Continued)

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Shih et al. 2019[103] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH | Source: Ø<br>Tube: Ø | Ø |
| Shin et al. 2017[104] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, $pO_2$, Bicarb, Na, K, Cl, glucose, lactate | Source: Ø<br>Tube: Ø | Described |
| Shin et al. 2020[105a] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: physician, nurse, paramedic | Stage: Ø<br>Serial: no | pH, $pCO_2$, $pO_2$, Bicarb, Na, K, Cl, Cr, glucose, ionized Ca, lactate, Hg, Hct | Source: arterial, venous, capillary<br>Tube: heparin | Described |
| SOS-KANTO 2017[107a] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | Lactate, ammonia | Source: Ø<br>Tube: Ø | Ø |
| Spindelboeck et al. 2013[108] | Europe | Retrospective cohort | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: physician | Stage: intra-arrest<br>Serial: no | $pO_2$ | Source: arterial<br>Tube: Ø | Described<br>Time: 1 min |
| Spindelboeck et al. 2016[109] | Europe | Prospective cohort | Age: Ø<br>Subtype: none | Setting: prehospital<br>Clinician: physician | Stage: intra-arrest, post-ROSC<br>Serial: no | pH, $pO_2$, $pCO_2$, BE | Source: arterial<br>Tube: Ø | Described<br>Time: 1 min |
| Su et al. 2008[111] | Asia | Retrospective cohort | Age: adult<br>Subtype: elderly | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, Hg, glucose, K troponin-I | Source: Ø<br>Tube: Ø | Ø |
| Su et al. 2009[112] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, glucose, Cr, Hg, K | Source: Ø<br>Tube: Ø | Ø |
| Tallman et al. 2017[114a] | Americas | Prospective cohort | Age: adult, peds<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | pH, $pCO_2$, $pO_2$, Bicarb, BE, Na, K, glucose, lactate | Source: venous, osseous<br>Tube: Ø | Described |
| Weil et al. 1985[123a] | Americas | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED, hospital<br>Clinician: Ø | Stage: intra-arrest, post-ROSC<br>Serial: yes | pH, $pCO_2$, Bicarb, lactate, Na, K, Hg, osmolality | Source: arterial<br>Tube: heparin | Ø |
| Williams et al. 2016[124a] | Australia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: yes | Lactate | Source: arterial, venous<br>Tube: Ø | Ø |

*Note*: Symbol "Ø" denotes incomplete reporting of methods.

Abbreviations: ALT, aminotransferase; AST, aminotransferase; BE, base excess; Bicarb, bicarbonate; Ca, calcium; CK-MB, creatine kinase-myocardial band; Cl, chloride; Cr, creatinine; ED, emergency department; Hct, hematocrit; Hg, hemoglobin; K, potassium; Mag, magnesium; Na, sodium; $pCO_2$, partial pressure of carbon dioxide (arterial or venous); Plt, platelet; $pO_2$, partial pressure of oxygen (arterial or venous); WBC, white blood cell count.

[a]Incomplete reporting to assess all inclusion and exclusion criteria.

[b]Population subtype—VF/pVT: ventricular fibrillation or pulseless ventricular tachycardia; cardiac: suspected cardiac etiology of arrest; ECPR: extracorporeal cardiopulmonary resuscitation; refractory: cardiac arrest not responding to standard advanced life support; PE: suspected pulmonary embolism; witness: cardiac arrest witnessed by layperson or emergency medical services; CKD: chronic kidney disease; cold: accidental hypothermia; TTM: targeted temperature management; elderly: geriatric patients.

[c]Timing of blood sample collection—intra-arrest: while patient is pulseless; at ROSC: <5 min after return of spontaneous circulation; post-ROSC: >5 min after return of spontaneous circulation; at ToR: <5 min before or after termination of resuscitation; at ECPR: <5 min after starting ECPR; post-ECPR: >5 min after starting ECPR.

[d]For prehospital studies, time interval between blood collection and final processing.

**TABLE 2** Cardiac studies.

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Aarsetoy et al. 2018[11a] | Europe | Prospective cohort | Age: adult<br>Subtype: cardiac | Setting: prehospital, ED<br>Clinician: paramedic | Stage: Ø<br>Serial: no | hs-cTnT, NT-proBNP, copeptin | Source: venous<br>Tube: EDTA | Described<br>Time: 24–48 h |
| Aarsetoy et al. 2020[12] | Europe | Prospective cohort | Age: adult<br>Subtype: cardiac | Setting: prehospital, ED<br>Clinician: paramedic | Stage: intra-arrest, at ToR, post-ROSC<br>Serial: no | hs-cTnT, NT-proBNP, copeptin | Source: venous<br>Tube: EDTA | Ø<br>Time: 24–48 h |
| Cakmak et al. 2020[25] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Copeptin, hs-cTnT, CK-MB | Source: venous<br>Tube: heparin | Described |
| Lai et al. 2004[63a] | Americas | Prospective cohort | Age: adult<br>Subtype: none | Setting: Ø<br>Clinician: Ø | Stage: Ø<br>Serial: no | Troponin-T | Source: venous<br>Tube: citrate | Described |
| Nagao et al. 2004[81a] | Asia | Prospective cohort | Age: adult<br>Subtype: cardiac | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | BNP | Source: venous<br>Tube: EDTA + aprotinin | Described |
| Paradis et al. 1994[94a] | Americas | Intervention | Age: adult<br>Subtype: refractory | Setting: ED<br>Clinician: physician | Stage: intra-arrest<br>Serial: yes | Atrial natriuretic peptide | Source: arterial, venous<br>Tube: Ø | Described |
| Timilsina et al. 2022[116] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, BE, lactate, NT-proBNP, troponin | Source: Ø<br>Tube: Ø | Ø |

*Note*: Symbol "Ø" denotes incomplete reporting of methods.

Abbreviations: BE, base excess; BNP, brain natriuretic peptide; CK-MB, creatine kinase-myocardial band; ED, emergency department; EDTA, ethylenediaminetetraacetic acid; hs-cTnT, high sensitivity cardiac troponin T; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

[a]Incomplete reporting to assess all inclusion and exclusion criteria.

[b]Population subtype—VF/pVT: ventricular fibrillation or pulseless ventricular tachycardia; cardiac: suspected cardiac etiology of arrest; ECPR: extracorporeal cardiopulmonary resuscitation; refractory: cardiac arrest not responding to standard advanced life support; PE: suspected pulmonary embolism; witness: cardiac arrest witnessed by layperson or emergency medical services; CKD: chronic kidney disease; cold: accidental hypothermia; TTM: targeted temperature management; elderly: geriatric patients.

[c]Timing of blood sample collection—intra-arrest: while patient is pulseless; at ROSC: <5 min after return of spontaneous circulation; post-ROSC: >5 min after return of spontaneous circulation; at ToR: <5 min before or after termination of resuscitation; at ECPR: <5 min after starting ECPR; post-ECPR: >5 min after starting ECPR.

[d]For prehospital studies, time interval between blood collection and final processing.

the body of literature are widespread. Recommendations for future research are provided.

## 5.1 | Heterogeneity of study design

Although each study shared the common element of intra-arrest sampling for blood-based biomarkers, the collection of studies meeting inclusion and exclusion criteria demonstrated substantial variability in many aspects of study design. The fundamental structure of emergency medical services (EMS) in the geographic regions of Asia, Europe, and Americas vary with regards to the clinical provider leading the resuscitation (paramedic vs. physician) and the site of the resuscitation (on-scene vs. rapid transport to a hospital). These variables affect the capability to draw/analyze blood samples and the timing of blood draws relative to the start of resuscitation. Not only does this affect the logistics of conducting the study, but it also affects the "context of use," a concise description of how a biomarker is intended to be used, which is required by regulatory agencies such as the US FDA.[10] In addition, the pathophysiology of OHCA evolves throughout the resuscitation,

**TABLE 3** Cell counts, electrolytes, hepatic, and renal studies.

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Ahn et al. 2011[15] | Asia | Prospective cohort | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | K | Source: arterial<br>Tube: Ø | Ø |
| Asano et al. 2021[17a] | Asia | Retrospective cohort | Age: adult<br>Subtype: witness | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | WBC, Hg, Plt count, D-dimer, Cr, Na, K, troponin-I, CK | Source: Ø<br>Tube: Ø | Described |
| Balci et al. 2017[18] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Na, K, Cr, glucose, Hg, troponin | Source: Ø<br>Tube: Ø | Ø |
| Choi et al. 2020[30] | Asia | Retrospective cohort | Age: adult<br>Subtype: cardiac | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | K | Source: Ø<br>Tube: Ø | Ø |
| Gando et al. 1988[36] | Asia | Prospective cohort | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: yes | pH, total Ca, ionized Ca, total protein | Source: arterial<br>Tube: plain | Described |
| Gando et al. 1990[37] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: yes | pH, total protein, total Ca, ionized Ca | Source: arterial, venous<br>Tube: plain | Described |
| Han et al. 2021[46] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | CRP, delta neutrophil index, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio | Source: Ø<br>Tube: Ø | Described |
| Johnston and Murphy 2005[53] | Europe | Retrospective cohort | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | K | Source: arterial, venous<br>Tube: heparin | Described |
| Kasai et al. 2012[55a] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | Ammonia | Source: venous<br>Tube: heparin | Described |
| Kim et al. 2020[59] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | K, total Ca, ionized Ca, Mag, albumin, Phos, BUN, Cr | Source: Ø<br>Tube: Ø | Ø |
| Lin et al. 2013[66a] | Asia | Prospective cohort | Age: adult<br>Subtype: CKD | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | pH, Bicarb, Na, K, Cl, Cr, glucose, Ca, Mag, lactate, CRP, ammonia, troponin-T, CK-MB, CK, AST, ALT, WBC, Hg, Plt count | Source: Ø<br>Tube: heparin, potassium ethylenediaminete-traacetic acid | Described |
| Matsuyama et al. 2018[76a] | Asia | Retrospective cohort | Age: adult<br>Subtype: TTM | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | Albumin | Source: Ø<br>Tube: Ø | Ø |
| Nojima et al. 2022[86] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Ammonia | Source: Ø<br>Tube: Ø | Ø |

(Continues)

**TABLE 3** (Continued)

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Shida et al. 2020[101a] | Asia | Retrospective cohort | Age: adult<br>Subtype: cardiac | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | K | Source: Ø<br>Tube: Ø | Ø |
| Shida et al. 2022[102a] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | Na | Source: Ø<br>Tube: Ø | Ø |
| Tamura et al. 2019[115a] | Asia | Retrospective cohort | Age: adult<br>Subtype: cardiac | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | Cr | Source: Ø<br>Tube: Ø | Ø |
| Tsai et al. 2018[117] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pCO_2$, Cr, AST, Na, K, troponin-I, Bicarb, Hg, WBC | Source: Ø<br>Tube: Ø | Described |
| Urban et al. 1988[120] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, ionized Ca, total Ca | Source: arterial<br>Tube: heparin | Described |
| Yanagawa et al. 2009[126a] | Asia | Retrospective cohort | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | pH, $pCO_2$, $pO_2$, Bicarb, BE, Na, K, Cl, Cr, BUN, glucose, total Ca, Phos, total protein, albumin, total bilirubin, AST, ALT, GGT, Alk Phos, amylase, cholinesterase, CK, WBC, Hg, ammonia, Plt count | Source: Ø<br>Tube: Ø | Ø |
| Yune et al. 2015[128a] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: yes | Delta neutrophil index, BUN, Cr, WBC, Plt count, Hct | Source: Ø<br>Tube: Ø | Described |

*Note*: Symbol "Ø" denotes incomplete reporting of methods.

Abbreviations: Alk Phos, alkaline phosphatase; ALT, aminotransferase; AST, aminotransferase; Bicarb, bicarbonate; BUN, blood urea nitrogen; Ca, calcium; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; Cl, chloride; Cr, creatinine; CRP, C-reactive protein; ED, emergency department; GGT, gamma-glutamyl transferase; Hct, hematocrit; Hg, hemoglobin; K, potassium; Mag, magnesium; Na, sodium; $pCO_2$, partial pressure of carbon dioxide (arterial or venous); Phos, phosphate; Plt, platelet; WBC, white blood cell count.

[a]Incomplete reporting to assess all inclusion and exclusion criteria.

[b]Population subtype—VF/pVT: ventricular fibrillation or pulseless ventricular tachycardia; cardiac: suspected cardiac etiology of arrest; ECPR: extracorporeal cardiopulmonary resuscitation; refractory: cardiac arrest not responding to standard advanced life support; PE: suspected pulmonary embolism; witness: cardiac arrest witnessed by layperson or emergency medical services; CKD: chronic kidney disease; cold: accidental hypothermia; TTM: targeted temperature management; elderly: geriatric patients.

[c]Timing of blood sample collection—intra-arrest: while patient is pulseless; at ROSC: <5 min after return of spontaneous circulation; post-ROSC: >5 min after return of spontaneous circulation; at ToR: <5 min before or after termination of resuscitation; at ECPR: <5 min after starting ECPR; post-ECPR: >5 min after starting ECPR.

[d]For prehospital studies, time interval between blood collection and final processing.

**TABLE 4** Coagulation, complement, and endothelium studies.

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Aarsetoy et al. 2021[13] | Europe | Prospective cohort | Age: adult<br>Subtype: cardiac | Setting: prehospital, ED, hospital<br>Clinician: paramedic | Stage: intra-arrest, at ToR, post-ROSC<br>Serial: yes | TAT, FXIa-AT, FIXa-AT | Source: venous<br>Tube: EDTA | Described<br>Time: 24–48 h |
| Bottiger et al. 1995[22] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: prehospital ED, hospital<br>Clinician: physician | Stage: intra-arrest, at ROSC, post-ROSC<br>Serial: yes | TAT, fibrin monomers, D-dimer, PAI-1 | Source: venous<br>Tube: citric acid + theophylline + adenosine + dipyridamole | Described<br>Time: 1 h |
| Bottiger et al. 2002[23] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: prehospital ED, hospital<br>Clinician: physician | Stage: intra-arrest, at ROSC, post-ROSC<br>Serial: yes | C3a, SC5b-9, neutrophil elastase, sP-selectin, sICAM-1 | Source: venous<br>Tube: EDTA | Described<br>Time: 1 h |
| Duvekot et al. 2015[35] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | TAT, tPA, PAI-1, TAFI, protein C, TEM, aPTT, PT-INR, fibrinogen, plasminogen, D-dimer, Hg, Plt function | Source: Ø<br>Tube: Ø | Described |
| Gando et al. 1997[39] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED, hospital<br>Clinician: Ø | Stage: intra-arrest, post-ROSC, at ToR<br>Serial: yes | Plt count, Plt function, 6-keto-PGF1$\alpha$, TXB2, 11-dehydro-TXB2 | Source: venous<br>Tube: citrate, EDTA + aprotinin + indomethacin | Described |
| Gando et al. 1997[40] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED, hospital<br>Clinician: Ø | Stage: intra-arrest, at ToR, post-ROSC<br>Serial: yes | Fibrinopeptide A, fibrinopeptide B, D-dimer, tPA activity, tPA antigen, PAI-1 activity, PAI-1 antigen | Source: arterial<br>Tube: citrate, heparin + aprotinin | Described |
| Gando et al. 1999[41] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED, hospital<br>Clinician: Ø | Stage: intra-arrest, at ToR, post-ROSC<br>Serial: yes | Tissue factor, tissue factor pathway inhibitor | Source: arterial<br>Tube: Ø | Described |
| Hostler et al. 2007[49] | Americas | Prospective cohort | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: physician | Stage: intra-arrest<br>Serial: no | TAT | Source: venous<br>Tube: citrate | Described<br>Time: Ø |
| Koami et al. 2017[60] | Asia | Retrospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Lactate, WBC, Hg, Plt count, PT-INR, aPTT, fibrinogen, FDP, D-dimer, TEM | Source: Ø<br>Tube: Ø | Described |

(Continues)

**TABLE 4** (Continued)

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Schochl et al. 2013[99] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: physician | Stage: intra-arrest<br>Serial: no | Hg, Hct, Plt count, PT-INR, aPTT, fibrinogen, TEM | Source: venous<br>Tube: EDTA, citrate | Described<br>Time: 2 h |

*Note*: Symbol "Ø" denotes incomplete reporting of methods.

Abbreviations: aPTT, activated partial thromboplastin time; C3a, complement component C3a; ED, emergency department; EDTA, ethylenediaminetetraacetic acid; FDP, fibrin degradation products; FIXa-AT, activated factor IX-antithrombin; FXIa-AT, activated factor XI-antithrombin; Hct, hematocrit; Hg, hemoglobin; PGF1α, prostaglandin F1alpha; Plt, platelet; PT-INR, prothrombin time and international normalized ratio; SC5b-9, complement SC5b-9 soluble membrane attack complex; sICAM-1, soluble intercellular adhesion molecule-1; sP-selectin, soluble P-selectin; TAFI, thrombin activatable fibrinolysis inhibitor; TAT, thrombin–antithrombin complex; TEM, thromboelastometry; tPA, tissue plasminogen activator; TXB2, thromboxane B2; WBC, white blood cell count.

[a] Incomplete reporting to assess all inclusion and exclusion criteria.

[b] Population subtype—VF/pVT: ventricular fibrillation or pulseless ventricular tachycardia; cardiac: suspected cardiac etiology of arrest; ECPR: extracorporeal cardiopulmonary resuscitation; refractory: cardiac arrest not responding to standard advanced life support; PE: suspected pulmonary embolism; witness: cardiac arrest witnessed by layperson or emergency medical services; CKD: chronic kidney disease; cold: accidental hypothermia; TTM: targeted temperature management; elderly: geriatric patients.

[c] Timing of blood sample collection—intra-arrest: while patient is pulseless; at ROSC: <5 min after return of spontaneous circulation; post-ROSC: >5 min after return of spontaneous circulation; at ToR: <5 min before or after termination of resuscitation; at ECPR: <5 min after starting ECPR; post-ECPR: >5 min after starting ECPR.

[d] For prehospital studies, time interval between blood collection and final processing.

so biomarker measurements occurring on-scene versus in the hospital may vary, even within a single patient.

While variation in time between collapse and the start of resuscitative efforts is an unavoidable reality of OHCA, studies still had significant heterogeneity in whether they accounted for the exact timing of blood draws relative to the start of resuscitation, whether the arrest was witnessed or not, and whether bystander CPR occurred, all of which may affect biomarker levels. Heterogeneity in the electrical activity of the heart (ie, ventricular fibrillation/tachycardia vs. PEA/asystole) not only defines interventions that may affect biomarker levels and context of use, but may also represent different underlying etiologies of arrest. Some studies included small cohorts of in-hospital cardiac arrest patients, which likely differ in underlying pathophysiology and whether biomarker levels are known prior to arrest. Finally, multiple evolutions of recommended intra-arrest management have occurred over the past 45 years, especially regarding chest compressions, ventilation, and medication administration. As a result, the ability to compare results from two technically similar studies performed in different decades is limited.

## 5.2 | Gaps in research

Few conclusions can be drawn from existing literature due to significant gaps that exist. The heterogeneity described above limits direct comparison between studies, and even when studies were relatively similar in study design, conflicting results were common. Missing data and lack of standardized reporting limits the reproducibility of many studies. This was especially true for the processes and methods used to collect, preserve, and measure blood-based biomarkers, which were missing from a surprisingly large number of studies. Even when "routine" laboratory studies were reported, the lack of blood source, tube additive, assay method, and measurement device limits reproducibility and generalizability. Finally, the statistical methods used for analysis were both heterogenous, and at times, markedly flawed. For example, when adjusted analyses were performed, a linear relationship was often assumed, even though many "routine" biomarkers indicate pathophysiology when measured levels are high or low, with healthy levels in the middle.

This literature base also demonstrates a lack of recognition that the pathophysiology of a patient who is intra-arrest is fundamentally different than one who is post-ROSC or on extracorporeal support, as blood draws from these different cohorts were commonly combined into a single cohort. This issue was the main reason why we could not fully assess inclusion and exclusion criteria for 31 studies. Clinical guidelines recognize this difference by providing completely different treatment recommendations and flow diagrams.[1] Although not explicitly defined in clinical guidelines, there may also exist a pathophysiological difference between the immediate post-ROSC period that is dominated by cardiovascular instability and re-arrest rates up to 40% (generally seen in the prehospital setting and emergency department), versus the post-cardiac arrest syndrome of comatose patients

**TABLE 5** Genetics, hormones, inflammation, and lipid studies.

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Gando et al. 1999[42] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED, hospital<br>Clinician: Ø | Stage: intra-arrest, at ToR, post-ROSC<br>Serial: yes | sL-selectin, sP-selectin, neutrophil elastase, thrombomodulin, TNF$\alpha$, IL-1$\beta$ | Source: arterial<br>Tube: Ø | Described |
| Gando et al. 2000[43] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED, hospital<br>Clinician: Ø | Stage: intra-arrest, at ToR, post-ROSC<br>Serial: yes | sICAM-1, sVCAM-1, sE-selectin, neutrophil elastase, thrombomodulin | Source: arterial<br>Tube: Ø | Described |
| Havmoeller et al. 2014[47] | Americas | Prospective cohort | Age: adult<br>Subtype: VF | Setting: Ø<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Non-esterified free fatty acids | Source: Ø<br>Tube: plain | Described<br>Time: Ø |
| Ichikawa et al. 2021[50] | Asia | Prospective cohort | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Epinephrine, norepinephrine, dopamine, vasopressin, | Source: Ø<br>Tube: Ø | Described |
| Kim et al. 2019[58] | Asia | Retrospective cohort | Age: adult<br>Subtype: cardiac | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Total cholesterol | Source: Ø<br>Tube: Ø | Ø |
| Koizumi et al. 2020[61] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, $pO_2$, $pCO_2$, Bicarb, lactate, Na, K, WBC, glucose, TSH, free T3, free T4, ACTH, cortisol, GH, IGF-1, renin, aldosterone | Source: Ø<br>Tube: Ø | Described |
| Lindner et al. 1992[70] | Europe | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest, at ROSC, post-ROSC<br>Serial: yes | ACTH, cortisol, vasopressin, renin | Source: venous<br>Tube: plain | Described |
| Lindner et al. 1996[71] | Europe | Prospective cohort | Age: adult<br>Subtype: VF, witness | Setting: ED<br>Clinician: Ø | Stage: intra-arrest, at ROSC, post-ROSC<br>Serial: yes | Endothelin, epinephrine, norepinephrine, vasopressin, ACTH, cortisol | Source: venous<br>Tube: EDTA, heparin, glutathione | Described |
| Longstreth et al. 1996[73] | Americas | Retrospective cohort | Age: adult<br>Subtype: none | Setting: prehospital<br>Clinician: paramedic | Stage: at ROSC, at ToR<br>Serial: no | Total T4, total T3, free T3, reverse T3, TSH, free T4 index | Source: Ø<br>Tube: EDTA | Described<br>Time: Ø |
| Morisaki et al. 1991[80] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | pH, K, epinephrine, norepinephrine, cortisol | Source: Ø<br>Tube: EDTA | Ø |
| Narayanan et al. 2014[82] | Americas | Prospective cohort | Age: adult<br>Subtype: cardiac | Setting: prehospital<br>Clinician: paramedic | Stage: intra-arrest<br>Serial: no | Testosterone, estradiol | Source: venous<br>Tube: Ø | Described<br>Time: Ø |

(Continues)

**TABLE 5** (Continued)

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Oshima et al. 2019[92] | Asia | Prospective cohort | Age: adult<br>Subtype: cardiac | Setting: ED<br>Clinician: Ø | Stage: intra-arrest, at ROSC<br>Serial: no | Epinephrine, dopamine, norepinephrine, vasopressin | Source: Ø<br>Tube: Ø | Described |
| Paradis et al. 1991[93] | Americas | Interventional | Age: adult<br>Subtype: refractory | Setting: ED<br>Clinician: physician | Stage: intra-arrest<br>Serial: yes | Epinephrine | Source: arterial, venous<br>Tube: glutathione | Described |
| Schultz et al. 1993[100] | Americas | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED, hospital<br>Clinician: Ø | Stage: intra-arrest at ROSC, post-ROSC, at ToR<br>Serial: yes | Cortisol, ACTH | Source: venous<br>Tube: plain, EDTA | Described |
| Strohmenger et al. 1995[110] | Europe | Prospective cohort | Age: adult<br>Subtype: cardiac | Setting: ED<br>Clinician: Ø | Stage: intra-arrest, at ROSC, post-ROSC<br>Serial: yes | Prolactin, PGF2$\alpha$, 15-keto-13,14-dihydro-PGF2$\alpha$, 6-keto-PGF1$\alpha$, TXB2 | Source: venous<br>Tube: EDTA + indomethicin | Described |
| Sumiyoshi et al. 2021[113] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest, post-ROSC<br>Serial: yes | sPD-L1 | Source: arterial<br>Tube: Ø | Described |
| Wander et al. 2016[122a] | Americas | Retrospective cohort | Age: adult<br>Subtype: VF/pVT | Setting: prehospital<br>Clinician: paramedic | Stage: Ø<br>Serial: no | Micro-RNA | Source: venous<br>Tube: Ø | Described<br>Time: 48 h |
| Wortsman et al. 1993[125] | Americas | Prospective cohort | Age: adult<br>Subtype: refractory | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: yes | Epinephrine, norepinephrine | Source: arterial, venous<br>Tube: heparin + glutathione | Described |

*Note*: Symbol "Ø" denotes incomplete reporting of methods.

Abbreviations: ACTH, adrenocorticotropic hormone; Bicarb, bicarbonate; ED, emergency department; GH, growth hormone; IGF-1, insulin-like growth factor-1; IL-1$\beta$, interleukin-1 beta; K, potassium; Na, sodium; $pCO_2$, partial pressure of carbon dioxide (arterial or venous); PGF1$\alpha$, prostaglandin F1alpha; PGF2$\alpha$, prostaglandin F2alpha; $pO_2$, partial pressure of oxygen (arterial or venous); sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; sL-selectin, soluble L-selectin; sP-selectin, soluble P-selectin; sPD-L1, soluble programmed cell death-1 ligand; sVCAM-1, soluble vascular cell adhesion molecule-1; T3, triiodothyronine; T4, thyroxine; TNF$\alpha$, tumor necrosis factor alpha; TSH, thyroid-stimulating hormone; TXB2, thromboxane B2; WBC, white blood cell count.

[a]Incomplete reporting to assess all inclusion and exclusion criteria.

[b]Population subtype—VF/pVT: ventricular fibrillation or pulseless ventricular tachycardia; cardiac: suspected cardiac etiology of arrest; ECPR: extracorporeal cardiopulmonary resuscitation; refractory: cardiac arrest not responding to standard advanced life support; PE: suspected pulmonary embolism; witness: cardiac arrest witnessed by layperson or emergency medical services; CKD: chronic kidney disease; cold: accidental hypothermia; TTM: targeted temperature management; elderly: geriatric patients.

[c]Timing of blood sample collection—intra-arrest: while patient is pulseless; at ROSC: <5 min after return of spontaneous circulation; post-ROSC: >5 min after return of spontaneous circulation; at ToR: <5 min before or after termination of resuscitation; at ECPR: <5 min after starting ECPR; post-ECPR: >5 min after starting ECPR.

[d]For prehospital studies, time interval between blood collection and final processing.

**TABLE 6** Oxidative stress and neurologic studies.

| Study[a] | Region | Design | Population[b] | Setting and clinician drawing blood | Sample timing[c] | Blood biomarker(s) | Sample collection | Laboratory methods[d] |
|---|---|---|---|---|---|---|---|---|
| Ishikawa et al. 2021[51a] | Asia | Prospective cohort | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest, post-ROSC<br>Serial: no | Biological antioxidant potential, Diacron-reactive oxygen metabolites | Source: Ø<br>Tube: Ø | Described |
| Kim et al. 2018[57a] | Americas | Interventional | Age: adult<br>Subtype: none | Setting: ED<br>Clinician: paramedic | Stage: Ø<br>Serial: yes | Nitrite | Source: Ø<br>Tube: nitrite preservation solution | Ø |
| Song et al. 2010[106] | Asia | Prospective cohort | Age: Ø<br>Subtype: witness | Setting: ED<br>Clinician: Ø | Stage: intra-arrest, at ROSC<br>Serial: yes | S100B | Source: Ø<br>Tube: serum | Described |
| Turedi et al. 2009[118a] | Asia | Prospective cohort | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Ischemia-modified albumin, malondialdehyde | Source: venous<br>Tube: serum | Described |
| Turkdogan et al. 2012[119a] | Asia | Prospective cohort | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | Matrix metalloproteinase-9 | Source: venous, arterial<br>Tube: Ø | Described |
| Vitturi et al. 2020[121a] | Americas | Interventional | Age: Ø<br>Subtype: none | Setting: ED<br>Clinician: Ø | Stage: Ø<br>Serial: no | Nitrite, cGMP, nitrated conjugated linoleic acid | Source: Ø<br>Tube: nitrite preservation solution, heparin | Described |
| Yokobori et al. 2018[127] | Asia | Prospective cohort | Age: Ø<br>Subtype: cardiac | Setting: ED<br>Clinician: Ø | Stage: intra-arrest<br>Serial: no | NSE, S100B, pNF-H, IL-6 | Source: Ø<br>Tube: Ø | Described |

*Note*: Symbol "Ø" denotes incomplete reporting of methods.

Abbreviations: cGMP, cyclic guanosine monophosphate; ED, emergency department; IL-6, interleukin-6; NSE, neuron-specific enolase; pNF-H, phosphorylated neurofilament heavy subunit; S100B, S100 calcium-binding protein beta.

[a]Incomplete reporting to assess all inclusion and exclusion criteria.

[b]Population subtype—VF/pVT: ventricular fibrillation or pulseless ventricular tachycardia; cardiac: suspected cardiac etiology of arrest; ECPR: extracorporeal cardiopulmonary resuscitation; refractory: cardiac arrest not responding to standard advanced life support; PE: suspected pulmonary embolism; witness: cardiac arrest witnessed by layperson or emergency medical services; CKD: chronic kidney disease; cold: accidental hypothermia; TTM: targeted temperature management; elderly: geriatric patients.

[c]Timing of blood sample collection—intra-arrest: while patient is pulseless; at ROSC: <5 min after return of spontaneous circulation; post-ROSC: >5 min after return of spontaneous circulation; at ToR: <5 min before or after termination of resuscitation; at ECPR: <5 min after starting ECPR; post-ECPR: >5 min after starting ECPR.

[d]For prehospital studies, time interval between blood collection and final processing.

**TABLE 7** Summary of studies and biomarkers.

| Characteristic | All studies ($n = 118$) | Studies with full reporting of inclusion-exclusion criteria ($n = 87$) |
|---|---|---|
| Year of publication, *n* (%) | | |
| 1970–1979 | 1 (1%) | 1 (1%) |
| 1980–1989 | 9 (8%) | 7 (8%) |
| 1990–1999 | 17 (14%) | 16 (18%) |
| 2000–2009 | 20 (17%) | 13 (15%) |
| 2010–2011 | 40 (34%) | 28 (32%) |
| 2020–present | 31 (26%) | 22 (25%) |
| Region, *n* (%) | | |
| Americas | 24 (20%) | 16 (18%) |
| Europe | 28 (24%) | 25 (29%) |
| Asia | 63 (53%) | 45 (52%) |
| Australia | 3 (3%) | 1 (1%) |
| Study design, *n* (%) | | |
| Retrospective cohort | 43 (36%) | 29 (33%) |
| Prospective cohort | 68 (58%) | 54 (62%) |
| Interventional | 7 (6%) | 4 (5%) |
| Patient age, *n* (%)[a] | | |
| Adult | 100 (85%) | 76 (87%) |
| Pediatric | 3 (3%) | 1 (1%) |
| Not reported | 17 (14%) | 11 (13%) |
| Subtype[b], *n* (%)[a] | | |
| VF/pVT | 5 (4%) | 4 (5%) |
| Cardiac | 16 (14%) | 12 (14%) |
| ECPR | 4 (3%) | 3 (3%) |
| Refractory | 3 (3%) | 2 (2%) |
| PE | 2 (2%) | 0 (0%) |
| Witness | 4 (3%) | 3 (3%) |
| CKD | 1 (1%) | 0 (0%) |
| Cold | 2 (2%) | 1 (1%) |
| TTM | 1 (1%) | 0 (0%) |
| Elderly | 1 (1%) | 1 (1%) |
| None | 80 (68%) | 62 (71%) |
| Setting of sample collection, *n* (%)[a] | | |
| Prehospital | 22 (19%) | 20 (23%) |
| Emergency department | 94 (80%) | 66 (76%) |
| Hospital | 14 (12%) | 12 (14%) |
| Not reported | 3 (3%) | 2 (2%) |
| Clinical provider collecting sample, *n* (%)[a] | | |
| Paramedics | 11 (9%) | 7 (8%) |
| Nurse | 2 (2%) | 1 (1%) |
| Physician | 17 (14%) | 14 (16%) |
| Not reported | 92 (78%) | 67 (77%) |
| Timing of sample collection[c], *n* (%)[a] | | |
| Intra-arrest | 90 (76%) | 84 (97%) |
| At ROSC | 12 (10%) | 12 (14%) |
| Post-ROSC | 20 (17%) | 18 (21%) |
| At ToR | 11 (9%) | 11 (13%) |
| At ECPR | 2 (2%) | 1 (1%) |
| Post-ECPR | 1 (1%) | 1 (1%) |
| Not reported | 25 (21%) | 0 (0%) |
| Serial samples, *n* (%) | | |
| Yes | 36 (31%) | 31 (36%) |
| No | 82 (69%) | 56 (64%) |
| Blood source, *n* (%)[a] | | |
| Venous | 37 (31%) | 26 (30%) |
| Arterial | 43 (36%) | 36 (41%) |
| Intraosseous | 1 (1%) | 0 (0%) |
| Capillary | 2 (2%) | 1 (1%) |
| Not reported | 52 (44%) | 35 (40%) |
| Blood tube additive described, *n* (%) | | |
| Yes | 45 (38%) | 33 (38%) |
| No | 73 (62%) | 54 (62%) |
| Laboratory methods and timing described, *n* (%) | | |
| Yes | 71 (60%) | 55 (63%) |
| No | 47 (40%) | 32 (37%) |
| Biomarker category[d], *n* (%)[a,e] | | |
| Diagnostic | 61 (58%) | – |
| Monitoring | 40 (38%) | – |
| Response | 15 (14%) | – |
| Predictive | 1 (1%) | – |
| Prognostic | 97 (92%) | – |
| Safety | 0 (0%) | – |
| Surrogate endpoint | 0 (0%) | – |
| Susceptibility | 0 (0%) | – |

[a]Options not mutually exclusive (sum can be >100%).

[b]Population subtype—VF/pVT: ventricular fibrillation or pulseless ventricular tachycardia; cardiac: suspected cardiac etiology of arrest; ECPR: extracorporeal cardiopulmonary resuscitation; refractory: cardiac arrest not responding to standard advanced life support; PE: suspected pulmonary embolism; witness: cardiac arrest witnessed by layperson or emergency medical services; CKD: chronic kidney disease; cold: accidental hypothermia; TTM: targeted temperature management; elderly: geriatric patients.

[c]Timing of blood sample collection—intra-arrest: while patient is pulseless; at ROSC: <5 min after return of spontaneous circulation; post-ROSC: >5 min after return of spontaneous circulation; at ToR: <5 min before or after termination of resuscitation; at ECPR: <5 min after starting ECPR; post-ECPR: >5 min after starting ECPR.

[d]Biomarker category—diagnostic: presence of disease or subtype; monitoring: draw repeatedly to assess disease status; response: demonstrate biologic response to medical intervention; predictive: predict favorable or unfavorable effect from medical intervention; prognostic: predict likelihood of clinical outcome; safety: adverse event after medical intervention; surrogate endpoint: predicts a specific clinical benefit; susceptibility: potential for developing a disease not currently present.

[e]Denominator is the total number of biomarkers ($n = 105$).

that is dominated by metabolic failure and uncontrolled inflammatory response (generally seen in the intensive care unit).[6]

Although this scoping review identified 105 different biomarkers that have been studied, the median number of studies per biomarker was only 2. Thus, for most biomarkers, it is not possible to draw conclusions regarding their utility in OHCA patients. Pediatrics is almost entirely absent from this field of research, with only three studies enrolling pediatric patients. Extrapolating adult literature to pediatric patients is problematic since the underlying etiologies of arrest likely differ in incidence and pathophysiology. Many studies seemed to evaluate what was readily available instead of actively looking for novel biomarkers, which may have resulted in observational bias (ie, "streetlight effect"). To date, there have been no systematic investigations designed to discover blood-based biomarkers with utility during the intra-arrest phase of OHCA. Two longitudinal studies have collected blood samples from OHCA patients in the prehospital settings, but both were focused on studying risk factors for OHCA, not intra-arrest management, with blood samples frequently collected late in the resuscitation when the patient was "stable" or after termination of resuscitation.[129,130]

## 5.3 | Recommendations for future research

Blood-based biomarkers play a central role in the diagnosis and treatment of essentially all critically ill patients, yet none are routinely measured during the intra-arrest phase of OHCA resuscitations. This scoping review makes clear the need for careful planning of future studies on intra-arrest blood-based biomarkers for OHCA to advance this field of research.

Specifically, we recommend in future studies that the timing of blood draws relative to key resuscitation events be reported, such as the time of collapse or recognition, EMS arrival, therapeutic interventions, ROSC, termination of resuscitation, and bystander interventions. Investigators should avoid phrases such as "after resuscitation," "in survivors," "on admission," "post-cardiac arrest," and "as soon as possible," as they have no uniform temporal or pathophysiological definition and can be interpreted differently depending on context and culture. The "context of use" for the biomarker under investigation should be explicitly stated, especially regarding whether it is to be used intra-arrest, immediately post-ROSC, or for post-cardiac arrest syndrome. Biomarker categories other than "prognostic" and "diagnostic" should be investigated. For example, "response" and "predictive" biomarkers could help guide the development and specificity of novel interventions. Serial blood draws should be obtained when possible, to determine which biomarkers are rapidly changing (possibly due to the pathophysiology of OHCA) versus those that are static (may have existed pre-arrest). Methods used to collect, process, preserve, and measure blood-based biomarkers, including tube additive, assay method, and device used to measure levels, should be universally reported. Finally, statistical models should not assume a linear relationship between biomarker levels and pathophysiology, unless well defined in prior research.

Since OHCA occurs outside the traditional setting for blood-based biomarker investigations, additional research is needed to develop novel processes and methods to collect, process, and analyze blood-based biomarkers in the prehospital setting. Systematic investigations designed to discover novel blood-based biomarkers for OHCA should also be undertaken. Finally, blood-based biomarker research that specifically targets pediatric OHCA is needed.

In conclusion, over 45 years of resuscitation science on intra-arrest blood-based biomarkers for OHCA have been conducted, yet heterogeneity of study design and gaps in the body of literature are widespread. Recommendations for future research are provided.

## AUTHOR CONTRIBUTIONS

Justin Benoit and Jason McMullan conceived the study and obtained research funding. Justin Benoit designed the study protocol. Justin Benoit and Andrew Hogan designed the data extraction templates. Justin Benoit, Andrew Hogan, and Katherine Connelly performed the literature search, data extraction, and data charting. Justin Benoit and Andrew Hogan performed data synthesis. Jason McMullan supervised the conduct of the study. Justin Benoit and Andrew Hogan drafted the manuscript, and all authors contributed substantially to its revision. Justin Benoit takes responsibility for the paper as a whole.

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## CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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