**Multimedia Appendix 4.** Evaluation of hypotheses to overcome the challenge of the lack of reliable biomarkers in cardiotoxicity research.

| Hypotheses | Novelty | Keywords | Publications (n=54), n (%) | Evaluator 1[a] score | Evaluator 2[b] score | Evaluator 3[c] score | Group consensus score |
|---|---|---|---|---|---|---|---|
| 1. Utilizing multi-omics approaches (genomics, proteomics, metabolomics) to identify novel and reliable biomarkers for cardiotoxicity | Integration of multi-omics data for comprehensive biomarker discovery | "multi-omics," "genomics," "proteomics," "metabolomics," "biomarkers," "cardiotoxicity" | 0 (0) | 4 | 4 | 4 | 4 |
| 2. Developing CRISPR[d]-based screening methods to discover genes and pathways involved in cardiotoxicity, leading to the identification of new biomarkers | CRISPR-based gene and pathway discovery for new cardiotoxicity biomarkers | "CRISPR," "gene discovery," "pathway discovery," "biomarkers," "cardiotoxicity" | 0 (0) | 5 | 4 | 3 | 4 |

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| 3. Applying single-cell RNA sequencing to cardiac tissues to uncover specific gene expression profiles that serve as reliable biomarkers for cardiotoxicity | Single-cell RNA sequencing to identify specific gene expression profiles | "single-cell RNA sequencing," "gene expression," "biomarkers," "cardiotoxicity" | 1 (2) | 4 | 3 | 4 | 3 |
| 4. Investigating the role of non-coding RNAs (microRNAs, long non-coding RNAs) in cardiotoxicity to identify them as potential biomarkers | Role of non-coding RNAs as novel cardiotoxicity biomarkers | "non-coding RNAs," "microRNAs," "long non-coding RNAs," "biomarkers," "cardiotoxicity" | 1 (2) | 4 | 3 | 4 | 3 |
| 5. Conducting large-scale genome-wide association studies to find genetic variants associated with increased risk of cardiotoxicity, which | Large-scale GWAS to find genetic variants linked to cardiotoxicity risk[f] | "GWAS," "genetic variants," "cardiotoxicity | 1 (2) | 4 | 4 | 4 | 4 |

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| can be used as biomarkers. | | risk,” “biomarkers” | | | | | |
| 6. Using high-throughput proteomic screening of blood samples from patients treated with cardiotoxic drugs to identify protein biomarkers indicative of cardiotoxicity | High-throughput proteomics for identifying protein biomarkers in blood | “high-throughput proteomics,” “blood samples,” “protein biomarkers,” “cardiotoxicity” | 0 (0) | 4 | 4 | 4 | 4 |
| 7. Developing metabolomic profiles of patients undergoing treatment with cardiotoxic agents to identify metabolic biomarkers that predict cardiotoxicity | Metabolomic profiling to discover metabolic biomarkers | “metabolomics,” “metabolic profiling,” “biomarkers,” “cardiotoxicity” | 50 (93) | 3 | 2 | 4 | 2 |

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| 8. Investigating extracellular vesicles (exosomes) released by cardiomyocytes under stress to identify their molecular cargo as biomarkers for cardiotoxicity | Identification of molecular cargo in exosomes as biomarkers | "extracellular vesicles," "exosomes," "molecular cargo," "biomarkers," "cardiotoxicity" | 0 (0) | 4 | 4 | 3 | 4 |
| 9. Applying advanced glycomics to study changes in glycosylation patterns of cardiac proteins as biomarkers of cardiotoxicity | Advanced glycomics for changes in glycosylation patterns | "advanced glycomics," "glycosylation patterns," "biomarkers," "cardiotoxicity" | 0 (0) | 4 | 4 | 4 | 4 |
| 10. Utilizing artificial intelligence and machine learning to analyze large datasets from clinical trials to identify novel biomarkers for cardiotoxicity | AI[e] and machine learning to analyze large clinical datasets | "AI," "machine learning," "clinical datasets," | 0 (0) | 4 | 4 | 3 | 4 |

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| | | “biomarkers,” “cardiotoxicity” | | | | | |
| 11. Exploring the gut-heart axis to identify microbiota-derived metabolites that serve as biomarkers for cardiotoxicity | Microbiota-derived metabolites as biomarkers for cardiotoxicity | “gut-heart axis,” “microbiota-derived metabolites,” “biomarkers,” “cardiotoxicity” | 0 (0) | 4 | 4 | 4 | 4 |
| 12. Using integrative bioinformatics approaches to combine data from different omics studies to pinpoint robust biomarkers for cardiotoxicity | Integrative bioinformatics for combining multi-omics data | “integrative bioinformatics,” “multi-omics data,” “biomarkers,” “cardiotoxicity” | 0 (0) | 4 | 4 | 4 | 4 |

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| 13. Investigating the role of immune system activation and inflammation in cardiotoxicity to identify cytokines and other immune markers as reliable biomarkers | Immune system activation and inflammation markers as biomarkers | “immune system activation,” “inflammation markers,” “biomarkers,” “cardiotoxicity” | 1 (2) | 4 | 4 | 3 | 4 |
| 14. Developing high-sensitivity assays to detect post-translational modifications in cardiac proteins as early biomarkers of cardiotoxicity | High-sensitivity assays for post-translational modifications | “high-sensitivity assays,” “post-translational modifications,” “biomarkers,” “cardiotoxicity” | 0 (0) | 4 | 4 | 4 | 4 |
| 15. Applying lipidomics to profile changes in lipid composition in blood samples as biomarkers for cardiotoxicity | Lipidomics for profiling changes in lipid composition | “lipidomics,” “lipid composition,” “biomarkers,” “cardiotoxicity” | 0 (0) | 4 | 4 | 4 | 4 |

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| 16. Using longitudinal studies with repeated sampling to track changes in potential biomarkers over time in patients treated with cardiotoxic drugs | Longitudinal studies for tracking biomarker changes over time | "longitudinal studies," "repeated sampling," "biomarkers," "cardiotoxicity" | 0 (0) | 4 | 4 | 4 | 4 |
| 17. Investigating the epigenetic changes in cardiomyocytes exposed to cardiotoxic agents to identify DNA methylation or histone modification patterns as biomarkers | Epigenetic changes as biomarkers for cardiotoxicity | "epigenetic changes," "DNA methylation," "histone modifications, biomarkers," "cardiotoxicity" | 0 (0) | 4 | 4 | 4 | 4 |
| 18. Developing high-throughput screening assays to identify oxidative stress markers in cardiomyocytes as biomarkers for cardiotoxicity | High-throughput assays for oxidative stress markers | "high-throughput screening," "oxidative stress markers," | 0 (0) | 5 | 5 | 3 | 5 |

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| | | “biomarkers,” “cardiotoxicity” | | | | | |
| 19. Exploring the role of cell-free DNA and RNA in the blood as non-invasive biomarkers for early detection of cardiotoxicity | Cell-free DNA and RNA as non-invasive biomarkers | “cell-free DNA,” “cell-free RNA,” “non-invasive biomarkers,” “cardiotoxicity” | 0 (0) | 4 | 4 | 4 | 4 |
| 20. Utilizing 3D bioprinted cardiac tissue models to study molecular changes under drug exposure and identify reliable biomarkers for cardiotoxicity | 3D bioprinted models for studying molecular changes | “3D bioprinted models,” “molecular changes,” “biomarkers,” “cardiotoxicity” | 0 (0) | 5 | 5 | 4 | 5 |

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[b]Author TG (MD, final-year PhD candidate).

[c]Author CY (MD, first-year PhD student).

[d]CRiSPR: clustered regularly interspaced short palindromic repeats.

[e]AI: artificial intelligence.

[f]GWAS: genome-wide association study.