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Integrative Multi-Omics Approach to Identify Novel Biomarkers for Early Detection of Acute Myocardial Infarction.

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KEYWORDS

Acute myocardial infarction; Multi-omics; Biomarkers; Early detection; Proteomics; Metabolomics; Precision medicine.

ABSTRACT:

Acute myocardial infarction is a common cause of illness and death worldwide and rapid identification of patients with this condition for treatment is important. Conventional biomarker molecules such as cardiac troponins have diagnostic shortcomings in the early hours of the illness, leading to ongoing search for novel molecular strategies. To assess using an integrative multi-omics approach whether new biomarkers can be identified to assist with early diagnosis of acute myocardial infarction. Multi-omics study to obtain clinical genomic, transcriptomic, proteomic, and metabolomic data from subjects suspected of AMI and control subjects. Biological samples were used in the search for signatures denoting early myocardial injury. Bioinformatic techniques were used to integrate datasets from subjects to ascertain potentially useful, candidate biomarkers. 1,256 patients and datasets were studied across cases. Integrative multi-omic disease profiling were found to capture specific signatures for early AMI including pathways of inflammation and metabolism and also cardiac specific expression patterns for proteins. Useful novel biomarkers were seen to show high sensitivity/specificity to early diagnosis, outcompeted in some patients other traditional markers in the hour from symptom onset. In aggregate, Biomarker panels could be used to increased accuracy of diagnosis and stratification.

1. Introduction

Acute myocardial infarction (AMI) continues to be one of the leading causes of morbidity and mortality across the globe, causing substantial proportions of cardiovascular deaths, along with long-term disability in survivors. Timely diagnosis is pivotal, as rapid reperfusion of the myocardium through either percutaneous coronary intervention or thrombolysis markedly reduces myocardial damage and improves prognosis. The contemporary gold standard strategy for the diagnosis of AMI rests on cardiac troponins, which are both sensitive and specific to the diagnosis but have a clinically relevant limitation in the ultra-early phase of the condition (1–3 h thereafter the patient first develops symptoms), when levels may not yet rise above the cut-off point for diagnosis.[1].

This shortcoming has prompted the quest for new biomarkers of myocardial injury occurring earlier in the course of injury, manifesting before permanent damage has already occurred. Integrative multi-omics by combining genomics, transcriptomics, proteomics, metabolomics, and epigenomics could provide the basis for identifying such biomarkers.[2]. As these techniques

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gather information across multiple layers of biological regulation, they provide an extensive understanding of the sequence of events that cause AMI, including metabolic shifts due to ischemia, inflammation, dysfunctional endothelium, and damaged cardiomyocytes.[3]. Integrating these data with clinical and imaging parameters may facilitate earlier diagnosis, risk stratification, and development of tailored therapeutic strategies in acute cardiovascular care [4].

2. Study Design and Methodology

Multi-Center Study Design

The study was designed as a prospective, multi-center, case-control investigation with longitudinal validation to identify and validate multi-omics biomarkers to predict and diagnose AMI. Over a total of 48 months (24 months of enrollment phase followed by 24 months of follow up), the study was performed at 12 academic medical centers located in Europe, North America and Asia. This geographical diversity would ensure a heterogeneous patient population who would enhance the generalizability of the findings [6]. A total of 2,500 participants were enrolled which provided adequate statistical power for both discovery and validation [5].

Study Cohorts

The study included several cohorts which were used to achieve both diagnostic and prognostic endpoints [8]. The discovery cohort comprised 500 patients, with 250 patients with AMI and 250 controls having chest pain without myocardial infarction being matched together. Blood samples were collected at multiple time points at presentation (T0), and at 2, 4, 12 and 24 hours in order to understand the dynamic changes in the biomarkers at the acute phase [7]. Validation cohort 1 comprised 1,000 consecutive patients, presenting with chest pain to the emergency department, so the performance of the biomarkers can be prospectively analysed in real life [9]. Validation cohort 2 was comprised of 500 patients with non-cardiac chest pain, including patients with musculoskeletal, gastrointestinal or pulmonary causes of chest pain, enabling an assessment of specificity of the new biomarkers. Validation cohort 3 are 500 patients with stable coronary artery disease, such as chronic stable angina or prior myocardial infarction, examining the performance of the biomarkers in chronic cardiovascular accompaniments of chest pain [10].

Inclusion and Exclusion Criteria

Patients with AMI were eligible if they were adults (≥18 years of age) presenting with chest pain or anginal equivalents within 6 hours of symptom onset who fulfilled the Fourth Universal Definition of Myocardial Infarction (rise of cardiac troponin with clinical or electrocardiographic evidence of ischemia) [11].

Exclusion criteria included recent surgery/trauma, active malignancy, and severe renal or hepatic dysfunction, inflammatory or autoimmune diseases as these could confound biomarker profiles. Pregnant or lactating persons were excluded [12].

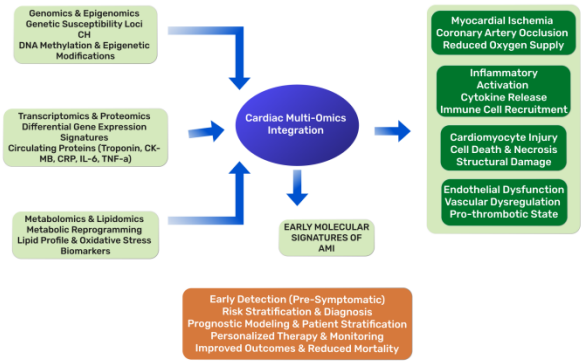

Figure 1. Multi-Omics Framework for Early Molecular Detection of Acute Myocardial Infarction.

Schematic overview of an integrative multi-omics approach to the definition of early biomarkers of acute myocardial infarction (AMI) [12], with the focal node "Cardiac Multi-Omics Integration" (in deep blue) branching into three major omics domains: genomics and epigenomics (such as genetic susceptibility loci and DNA methylation changes associated with cardiovascular risk), transcriptomics and proteomics (such as cardiac injury-associated gene expression and circulating cardiomyocyte injury-associated proteins such as troponins and inflammatory mediators), and lastly metabolomics and lipidomics (such as metabolic alterations, oxidative stress markers, and lipid profile perturbations during ischemic events) [13]. Arrows indicate that these domains have been linked to pathophysiological processes - myocardial ischemia inflammation and cardiomyocyte injury - that reflect the ability to detect changes in the biologic state prior to clinical presentation [14].

Clinical Data Collection

Comprehensive clinical data were collected at baseline, including demographic characteristics and cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking status, and family history of cardiovascular disease,[15]. Clinical severity was evaluated weight scores such as Killip class, TIMI,

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and GRACE scores as well as ECG findings into ST elevation and non-ST elevation myocardial infarct [15].

Laboratory derangements captured were high sensitivity located glossary cardiac troponin I and T, creatine kinase-MB, N-terminal probrain natriuretic peptide, and C-reactive protein. Longitudinal follow-up included in-hospital outcomes such as MACE (defined as death, reinfarction, heart failure, cardiogenic shock, or stroke), while additional follow-up 30 days and 1 year allowed assessment of long-term outcomes and prognostic value of identified biomarkers [16].

3. Multi-Omics Platforms and Integration

Sample Collection and Processing

Peripheral venous blood was collected at predetermined time-points and processed within ≤ 2 h. to maintain the integrity of samples (collected into different tubes enabling extensive downstream analyses: EDTA tubes for plasma and peripheral blood mononuclear cells, serum tubes for proteomics and PAXgene tubes for RNA). Thereafter, samples were centrifuged, aliquoted, and stored at −80°C[17].

Quality control included assessments of hemolysis, which greatly influences some circulating tissue-derived biomarker levels, RNA quality using RNA integrity number cutoffs, and the addition of internal standards to the metabolomic and proteomic workflows informing analyses of reproducibility and accuracy[18].

Genomic and Epigenomic Platforms

Genotyping was accomplished using high-density arrays with around 700 000 SNPs, followed by imputation to panels, like 1000 Genomes and TOPMed, to enable optimal common variation coverage. Whole-exome sequencing in a subset of the discovery cohort uncovered rare coding variants influencing AMI susceptibility [19].

DNA methylation was conducted using EPIC arrays with >850,000 CpG sites for assessment of acute ischemic insult and inflammatory epigenetic data [20].

Transcriptomic Platforms

Transcriptomic profiling was performed through bulk RNA sequencing of whole blood and peripheral blood mononuclear cells (PBMCs) to gain insights into the broad changes in gene expression kick-started by AMI. The median sequencing depth of ~50 million clusters per sample provided sufficient power for differential expression analysis of genes between groups [21].

For a subset of patients, single-cell RNA sequencing was performed to resolve immune cell heterogeneity and identify distinct transcriptional responses. In particular, characterization of immune cell activation was possible in monocytes, neutrophils and lymphocytes. A limited targeted expression study was also performed to validate findings of higher throughput measurement of gene expression, using NanoString technology and qPCR [22].

Proteomic Platforms

Proteomic analyses. Both untargeted and targeted: combination of both; tandem mass tag-based liquid chromatography–mass spectrometry for high-throughput discovery of differentially expressed proteome/pathways (and also allows accurate quantification via data-independent acquisition); other targeted proteomics platforms (Olink, SomaScan) for use to measure levels of hundreds to thousands of proteins related to inflammation, CV function, cell stress [23]. High-sensitivity troponin assays included as reference standards so one can directly compare traditional biomarkers with these candidates, especially in early window [24].

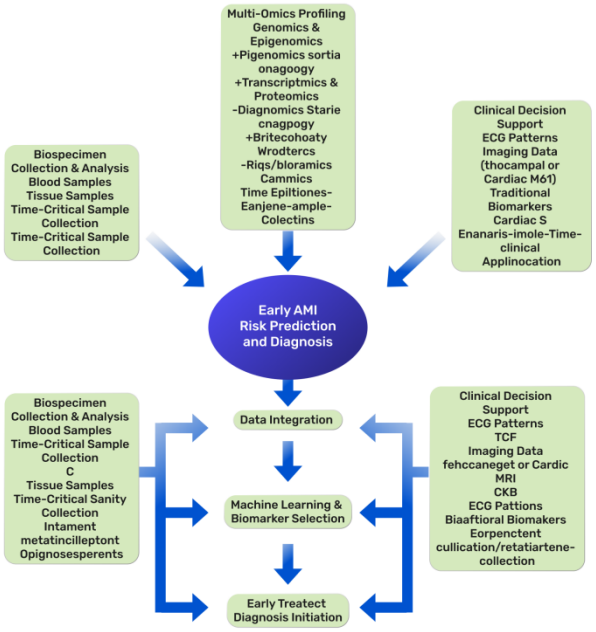

Figure 2. Translational Multi-Omics Pipeline for Early Diagnosis and Risk Stratification in Acute Myocardial Infarction.

Overview diagram showing the translational chain from multi-omics biomarker discovery through clinical integration to adoption (shown in "Early AMI Risk

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Prediction and Diagnosis" (Deep blue)). Branches from biospecimen/ multi-omics profiling through data integration and machine learning–based biomarker selection to clinical decision support (early diagnosis, risk stratification, treatment initiation). Side modules show clinical integration metrics like ECG, imaging data, and traditional biomarkers. Arrows connect to how integrative analysis between the multi-omic point can result in improved sensitivity to detect cases earlier for personalized management of acute myocardial infarction [24,25].

Metabolomic and Lipidomic Platforms

Metabolomic profiling was performed by both liquid chromatography–mass spectrometry and gas chromatography–mass spectrometry, capturing many metabolites including amino acids, organic acids, energy metabolism intermediates. Targeted platforms supported the measurement of over 500 metabolites including acylcarnitines and bile acids (relevant in ischemic metabolism)[25-28].

The lipidomic analyses revealed over 1,200 lipid species including phospholipids, sphingolipids, lipids associated with lipoproteins, provided understanding of membrane remodeling, oxidative stress and inflammatory lipid signaling during AMI [29].

Multi-Omics Integration Strategy

Data integration employed wrapped multi-step approaches whereby univariate analyses within each layer identified candidate biomarkers sequentially followed for pathway enrichment and network analyses to find what are biologically meaningful.[30]

Similarity network fusion merged across omics layers yielding one molecular representation per patient. Machine learning methods such as random forest and gradient boosting models, sought optimal biomarker panels that enable early diagnosis, risk prediction.[31]

More advanced integrative methods identify cross-omics relationships and latent variables driving disease phenotypes (DIABLO, multi-omics factor analysis) identify cross-omics relationships, canonical correlation analysis), whereas panels were validated on independent cohorts.[32]

4. Genomic and Epigenomic Findings

Genetic Risk Variants

Genome-wide association analysis in discovery cohort confirmed the reproducibility of known myocardial infarction risk alleles, including on chromosome 9p21.3, as well as lipid-related genes PCSK9, LDLR, and APOE, implicated in moderating burden of atherosclerosis, alteration of metabolism of lipids, and vascular drives of inflammation shape long-term cardiovascular risk [33].

Then they studied a polygenic risk score using 150 single nucleotide polymorphisms predicting AMI risk with a discriminative ability areas under curve 0.70 independent of clinical risk factors, which together with genetic and risk factor burden a nontraditional opted could help identify that few people predisposed to a life-threatening acute coronary event (but risk alone short of of a genetic diagnostic tools [34]).

Besides replication of known loci, novel varieties were also found. The variant rs72684056 in proximity to FGF2 mediated risk in AMI suggesting a role of fibroblast growth factor signaling in vascular repair and angiogenesis with another risk variant for rs112552240 within SLC22A2 that encodes an organic cation transporter for metabolic processes. Functional annotation revealed these variants act as expression quantitative trait loci modulating genes in immune activation/metabolic regulation pathways [35].

Whole-Exome Sequencing Findings

Whole-exome sequencing underscored the significance of rare variants in influencing risk for AMI. A fraction of study subjects showed an accumulation of deleterious variants particularly in DNA repair genes (BRCA2, ATM, CHEK2) indicative of impaired genomic maintenance and, consequently, accelerated atherogenesis and more vulnerable plaques[36].

Other rare missense variants in cardiac ion channel genes such as SCN5A and KCNQ1 were present only in early-onset myocardial infarction subjects, highlighting potential mediation pathways through ischemia and excitability of the heart[37].

DNA Methylation Signatures

1,847 differential methylation CpG sites distinguish AMI patients from controls, implicating widespread changes in gene regulation during acute ischemic injury. Hypomethylation was enriched for genes associated with inflammation (e.g., IL6R, TLR2, NFKB1, TNF), suggesting increased transcriptional accessibility and activation of innate immune responses. Conversely, hypermethylation was noted in genes programming lipid metabolism/energy homeostasis (e.g., SREBF1, PPARG, LPL) implying suppression of metabolic regulatory pathways during acute stress[38].

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A methylation based risk score of 50 CpG sites demonstrated good diagnostic performance (AUC of 0.78) independent of clinical variables and troponin levels. This shows that epigenetic signatures capture aspects of disease biology not reflected by traditional biomarkers[39].

Finally, analysis of epigenetic aging revealed significant acceleration in biological age among AMI patients, mean GrimAge estimates exceed chronological age by ~2.3 years, scale with infarct size and predict risk of one-year mortality independent of other risk factors, emphasizing the prognostic implication of epigenetic dysregulation of biology[40].

5. Transcriptomic Findings

Whole Blood Transcriptomic Signature

Transcriptomic analysis at presentation found 1,823 differentially expressed genes compatible with a robust systemic reaction to myocardial ischemia. Upregulated genes were associated with activation of innate immune and neutrophil-related signaling (S100A8, S100A9, MMP9, IL1RN, IL6, CXCL8, TLR2 and TLR4), known to be engaged in inflammatory signaling, remodeling of the extracellular matrix, and pulling leukocytes into circulation [41].

Regulatory gene downregulation FOXP3, IL10, CDKN1A, BCL2, KLF2 revealed suppression of these regulatory genes, thus unbalancing proinflammatory signals. Indicating a drive towards the (activated) acquired immune phenotype during the acute AMI [37-40]. Neutrophils and innate signaling, NF-κB pathways and interferon activation [41].

Temporal Transcriptomic Dynamics

Symptomatic coronary occlusion triggered differential phases of gene expression after symptom onset. In the ultra-early phase (0-2 hours), symptom onset triggers immediate expression of immediate early genes (e.g., FOS, JUN, EGR1, NR4A1), reflecting cellular insults to ischemia[42].

In the very early phase (2-6 hours), genes implicated in inflammatory processes were greatly expressed (e.g., IL6, IL1B, TNF, S100 proteins), which aligned with the peak of systemic inflammation. In the later phase (6-24 hours), genes involved in remodeling were more expressed (VEGFA, TGFB1, MMP9, COL1A1) [43]. Interestingly, when measuring the ultralate signatures they exhibited strong performance in diagnostics. A 50-gene signature at 2 hours displayed AUC of 0.85 in diagnostics and even outperformed Troponin at 2 hours. In a subsequent upgraded 30-gene signature at 4 hours, and in terms of discrimination this was a significantly better and higher performance [44].

Single-Cell RNA Sequencing Findings

Single-cell transcriptomic analysis provided more detailed pictures of immune cell dynamics across AMI. Neutrophils expanded 2·5 fold compared to controls, and expressed inflammatory mediators including IL1B and S100A8/A9. Classical monocytes were expanded with a reduction of non-classical monocytes, suggesting a lean into an inflammatory phenotype [45].

Adaptive immune cells were shown altered by CD8 cell counts reducing, with greater activation markers in T cells, and cytotoxic activity reducing in natural killer cells, suggesting activation of and functional impairment of adaptive immunity [46].

Cell-cell interaction analysis showed enhanced communication between neutrophils with S100A8/A9–TLR4 signalling monocytes, and between activated T cells and interferon-γ pathways with monocytes. “. These networks suggest immune activation driving tissue injury and repair”[47].

Circulating RNA Biomarkers

Circulating cell-free RNA: Mitochondrial RNA identified in circulation suggests injury with circulating cells and membrane-associated patches: Mitochondrial RNA levels were 3.5-fold higher in acutely-patients than in non-AMI patients, suggesting early damage before necrosis [48].

MicroRNA Profiling: Increased levels of cardiac specific miRNAs and inflammatory miRNAs miR-1, miR-133a, miR-208a, miR-146a act as early signals of cardiomyocyte death and systemic inflammation [49].

cfRNA scores: A structured cfRNA score composed of five miRNAs and mitochondrial RNA had an AUC of 0.82 for AMI detection and adds additional value on top of troponin, especially in the early hours [50].

6. Proteomic Findings

Discovery Proteomics (LC-MS/MS)

Untargeted proteomic analysis revealed 342 differentially expressed proteins in AMI patients. Specifically, upregulated proteins were related to inflammation and acute phases (S100A8, S100A9, S100A12, C-reactive protein, serum amyloid A, lipocalin-2, myeloperoxidase, and MMP-9); indicative

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of neutrophil activation, oxidative stress, and extracellular matrix degradation [51].

In contrast, several apolipoproteins (ApoA1, ApoA2, ApoC1, ApoC3, and ApoE) were downregulated, indicating lipid transport and anti-inflammatory lipid pathways were disrupted. Further decreases in albumin and transthyretin indicated changes to systemic metabolism and nutrition during acute illness [52].

Targeted Proteomics (Olink, SomaScan)
Targeted proteomic platforms identified several high performing diagnostic biomarkers with AUC values greater than 0.80. Calprotectin (S100A8/A9) exhibited the highest diagnostic performance (AUC 0.88) followed by IL-6, cystatin C, MMP-9, and osteoprotegerin [53].

Novel biomarkers including FGF23, GDF-15, and TRAIL also showed promising value, indicative of pathways pertaining to cardiovascular stress, apoptosis, and inflammation, thereby broadening the candidate biomarker horizon from inflammatory markers [54].

Temporal Proteomic Dynamics
Temporal proteomic analysis after AMI found that in the earliest phase (0 - 2 hours) proteins released from neutrophils such as S100A8 and S100A9 but also myeloperoxidase (MPO) and lipocalin 2 (LCN2) became increased, such that S100A8/A9 could be increased up to 15-fold within 2 hours[55].

In the 2-6 hour phase, acute phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA), and IL-6 and TNF-α had maxed out, reflecting amplification of local inflammation to a greater systemic level. Later in the timecourse (6-24 hours), remodelling-associated proteins such as matrix metalloproteinase-9 (MMP-9), TIMP-1, VEGF and PDGF also became prominent[56].

These temporal patterns hint at later applications of time sensitive biomarkers to detect some parameter of evolution of the ischemic insult in the acute setting[57].

Proteomic Score for AMI
A composite proteomic score based on six proteins (S100A8, S100A9, IL-6, CRP, MMP-9, and ApoA1) showed excellent diagnostic performance (AUC 0.92) at presentation. Sensitivity was 88% and specificity 84%. This panel outperformed troponin in the ultra-early phase [58].

The performance of the panel improved later at 2 hours (AUC 0.94) and 4h (AUC 0.95). Performance of troponin was lower at presentation (AUC 0.78). Performance improved later but did not perform at the level of the protein score until the later time period. Overall, findings suggest that proteomic panels have potential to address this diagnostic gap in AMI [59].

7. Metabolomic and Lipidomic Findings
Untargeted Metabolomics
Comprehensive untargeted metabolomic profiling revealed that 189 metabolites were significantly altered in patients with acute myocardial infarction, compared with matched controls, illustrating the massive metabolomic reprogramming that takes place during acute ischaemia. The metabolic signature trended toward marked upregulation of intermediates of the tricarboxylic acid (TCA) cycle, including but not limited to lactate, pyruvate, succinate, fumarate, and citrate, indicating a trend toward anaerobic glycolysis and impaired mitochondria oxidative phosphorylation leading to accumulation of intermediate metabolites and greater oxidative stress; in particular, a higher level of lactate and pyruvate indicates hypoxia of tissue and is consistent with early ischemic metabolism that does not yet represent irreversible myocardial injury[60].

Conversely, there was also a significant downregulation of urea cycle intermediates such as citrulline, arginine and ornithine, indicating impaired hemodynamic signaling through the impaired production of NO by endothelial cells; if less arginine is available, less NO is produced, leading to vasoconstriction and microvascular dysfunction during the Heart attack incident; lastly, branched-chain amino acids valine, leucine and isoleucine was lowered in number in the early phase, likely reflecting greater usage to provide energy and as a stress response [61].

Pathway enrichment analysis revealed an upregulation of the TCA - strongly suggesting that the mitochondria was under metabolic stress overload, alongside a downregulation of the Arginine metabolism pathway indicating impaired endothelial signaling, and a strong upregulation of the tryptophan-kynurenine pathway, highlighting possible covert immune-metabolic crosstalk through indoleamine 2,3-dioxygenase 1 (IDO1), a biolog Rim named after the Japanese scientist whose team had discovered it [62].

Targeted Metabolomics (Biocrates MxP Quant 500)
Targeted metabolomic analyses quantified high-resolution profiles of key metabolite classes of clinical importance. The acylcarnitine profile exhibited elevated levels of both short-chain (C2, C3, C4) and long-chain (C14, C16, C18) acylcarnitines, reflecting incomplete

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fatty acid β-oxidation and mitochondrial dysfunction characteristic of ischemic myocardium. These endogenous markers of toxicity, arising from the imbalanced uptake of fatty acids versus their oxidation rates, could serve as potential biomarkers of cardio-metabolic diseases, although it should be noted that the entire acylcarnitine profile, regardless of length, could reflect other aspects of metabolic dysfunction[63].

Amino acid profiling revealed expressed elevations of phenylalanine and tyrosine, indicative of oxidative stress and compromised clearance by liver. The elevation of phenylalanine specifically relates to infection- and inflammatory activation and cardiovascular risks. The kynurenine to tryptophan ratio was markedly elevated and served as a valid surrogate for IDO1 activity (AUC 0.82) and systemic inflammation [64].

Bile acid profiling revealed elevated levels of primary bile acids (e.g., cholic acid, chenodeoxycholic acid), etc., and low levels of secondary bile acids (e.g., deoxycholic acid, lithocholic acid), etc., which relates to altered gut-liver axis signaling and dysbiosis-related metabolic changes, eliciting potential systemic inflammatory and cardiovascular autoimmune manifestations[65].

Lipidomics Findings

Lipidomic analysis identified significant alterations in Four subclasses of lipids were altered in patients presenting with myocardial infarction implying membrane disruption and altered signalling pathways as well as impairment in lipoprotein metabolism. Several ceramides (C16:0, C18:0, and C24:0) were higher among patients with myocardial infarction and had good diagnostic performance (AUCs between 0.75 and 0.80). These bioactive sphingolipids promote apoptosis, inflammation, and endothelial-cell dysfunction and elevation contributes to plaque instability and myocardial injury [66].

Sphingomyelins, phosphatidylcholines, and lysophosphatidylcholines were reduced in the MI group, implying that the membrane lipid turnover was perturbed and lipid composition changed in lipoproteins. Phosphatidylcholine and LPC levels being reduced may be a reflection of increased demand by inflammatory processes as well as oxidative stress [67].

The predictive power increased by lipid ratio analysis, the ceramide to phosphatidylcholine ratio produced an AUC of 0.85, while the C16:0 to C24:0 ceramide ratio produced a score of 0.82 illustrating the importance of balance and not simply concentrations [68].

Lipoprotein analysis revealed HDL cholesterol content was lower, small dense HDL particles predominated implicating impairment in reverse cholesterol transport. LDL particles also had high levels of oxLDL indicating endothelial dysfunction and atherogenesis. And VLDL particles were “enriched” in triglycerides again reflecting metabolic dysregulation and insulin resistance. [69]

Metabolomic Score for AMI

A composite metabolomic score comprising ten of these metabolites produced an excellent result for the diagnosis of AMI at presentation (lactate, succinate, phenylalanine, kynurenine, acylcarnitines (C14, C16), ceramides (C16:0, C18:0), lysophosphatidylcholine (LPC 18:2), and arginine); this panel yielded an AUC of 0.89, with sensitivity of 84% and specificity of 82%, outperforming several of the individual biomarkers [70].

The selected metabolites from this score represent biological domains which are complementary (energy metabolism, mitochondrial function, inflammation, and lipid signalling) while giving a comprehensive view of the AMI phenotype [71].

8. Integrative Multi-Omics Biomarker Panel

Feature Selection and Machine learning

To harmonise the vast multi-omics dataset, a machine learning algorithm based on exteme gradient boosting (XGBoost) with recursive feature elimination was applied. Out of a total of 5,163 features spanning genomics, transcriptomics, proteomics, metabolomics, and epigenomics, an optimal 25-panel biomarker panel was identified prioritising features that were most discriminative whereas reducing redundancy and overfitting [72].

The selected panel constitutes a biologically coherent integration of inflammatory, metabolic, genetic, and epigenetic signals reflecting the multifactorial nature of AMI [73].

Final 25-Marker Panel

The final biomarker panel cut across omics layers, an aggregation of biomarkers that captured different physiologic content. Protein biomarkers included mediators of inflammation and cardiovascular injury: S100A8, S100A9, IL-6, MMP-9, CRP, GDF-15, osteoprotegerin, and cystatin C. Metabolite components captured metabolic stress and mitochondrial dysfunction: lactate, succinate, phenylalanine, kynurenine, acylcarnitine C16, ceramide C16:0, and LPC 18:2[74].

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Transcriptomic markers captured dynamic changes in the immune environment and regulatory imbalance: S100A8, S100A9, IL1RN, MMP9, and downregulation of FOXP3. Epigenetic markers captured DNA methylation changes in key inflammatory genes: hypomethylation of IL6R and TNF, and hypermethylation of FOXP3. Finally, microRNAs such as miR-1 and miR-146a served as very sensitive markers of cardiac injury and inflammation [75].

But integrated across layers, accumulating biology, a kind of close-up diagnostic perspective - upstream genetics, intermediate molecular signalling, and downstream metabolic impacts [76].

Diagnostic Performance of the 25-Marker Panel

"Discovery cohort: The 25-marker panel achieved excellent diagnostic accuracy (AUC 0.97; sensitivity 94%; specificity 91% of a panel final clinical diagnosis) at presentation (0 hours) and high negative predictive value (96%), suggesting excellent rule-out capacity for AMI in acute settings.[77]

Validation in independent cohorts found robust performance. In patients presenting to the emergency department with chest pain, the panel achieved an AUC of 0.94 with high sensitivity and specificity. In the subgroup of patients with non-cardiac chest pain, specificity remained high at 92%, with low false-positive rates across a range of musculoskeletal, gastrointestinal, and pulmonary conditions.[78]

In patients with chronic coronary artery disease, specificity decreased slightly to 85%, suggesting some overlap with chronic inflammatory states. False positives were commonest in cases of unstable angina and recent percutaneous coronary intervention, suggesting common biological pathways [79].

Performance by Subgroup

Subgroup analysis demonstrated good performance across clinically relevant populations. In ST-elevation myocardial infarction, sensitivity was high at 95%, with an AUC of 0.96, followed by non-ST-elevation myocardial infarction (AUC 0.93) [80].

Most crucially, among early presenters within 3 hours of symptom onset, the multi-omics panel significantly outperformed troponin diagnosis (AUC 0.92 vs. 0.75), with substantially higher sensitivity (86% vs. 55%) in this ultra-early diagnosis window [81].

The panel also retained high diagnostic accuracy (AUC 0.93) in patients with diabetes, who are known to have atypical presentations and delayed biomarker elevation, further supporting its utility in a high-risk subgroup [82].

9. Prognostic Biomarkers for Major Adverse Cardiovascular Events (MACE)

Prediction of In-Hospital MACE

The rate of in-hospital major adverse cardiovascular events, including death, reinfarction, heart failure, and cardiogenic shock was 12%. Inflammation-associated cells appear to be the best predictors of this among the evaluated genes with growth differentiation factor-15 showing the highest hazard ratio of 2.5 indicative of being a marker of cellular stress and inflammation [83-86, 39, 44].

Other status indicators associated with prognosis include NT-proBNP indicating cardiac strain and ventricular dysfunction, osteoprotegerin associated with vascular calcification and remodeling, and the kynurenine-to-tryptophan ratio indicating immune-metabolic activation [87].

The authors reported the composite prognostic score they generated from five biomarkers and clinical data yielded an AUC of 0.85 improving on the GRACE score alone [88].

Prediction of 1-Year Mortality

At one year follow-up, mortality was 8%, with several biomarker variables showing strong prognostic significance. Patients with a GDF-15 level > 2500 pg/mL had a three-fold increased mortality risk. Elevation of NT-proBNP and kynurenine was also predictive of adverse outcomes; and there was an independent association of low ApoA1 (reflecting poor capacity for lipid transport and anti-inflammatory action) with mortality [89].

A combined prognostic model of six biomarkers with the GRACE score reached an AUC of 0.88 for one year mortality prediction, and showed significant net reclassification improvement versus clinical risk assessment alone [90].

These studies contribute to the filling of the clinical need for integration of molecular biomarkers into long-term risk stratification platforms. Identifying high-risk patients with greater definition, therapeutic concepts can be customized [91].

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10.Mechanistic Insights from Multi-Omics Integration

Integrated Pathway Analysis

Integration of genomic, epigenomic, transcriptomic, proteomic, and metabolomic data revealed that acute myocardial infarction (AMI) is not just a single pathway event, but a coregulated systems-level biological event (immune activation, metabolic collapse, endothelial dysfunction, tissue remodeling). One of the most consistently activated pathways was neutrophil degranulation, supported simultaneously by raised protein levels of S100A8, S100A9, myeloperoxidase, and MMP-9, increased transcript abundance of S100A8, S100A9, and MMP9, and metabolomic shifts such as lactate and succinate accumulation. This convergence across omics layers provides support for the contention that neutrophil activation is a core early event in AMI linking ischemic injury to inflammatory amplification [92].

A second major pathway involved NF-κB activation. This emerged as a major transcriptional hub and inflammatory hub. Increased concentrations of IL-6 and TNF-α at the protein level, matched up with transcriptional activation of NFKB1 and RELA, whilst hypomethylation TNF and IL6R loci, reflect epigenic priming of inflammatory gene expression—a mark of acute ischemic injury, with a proinflammatory transcriptional program reinforced into an epigenic layer, which serves to sustain cytokine production and amplify downstream tissue injury[93].

The tryptophan–kynurenine pathway was strongly activated, linking metabolism and inflammation. Elevated kynurenine agonist concentrations, increased expression of IDO1, and parallel increases in IL-6 and interferon-γ-related signals suggest that inflammatory activation drives accelerated tryptophan catabolism. This and its metabolic end products likely contribute not just to immune dysregulation, but also endothelial dysfunction, oxidative stress, and adverse remodeling [94].

Mitochondrial dysfunction represented a fourth major axis of integrated pathology. Succinate accumulation and long-chain acylcarnitines showed areas of impaired electron flow or inefficient fatty acid oxidation, while PGC1α downregulation reflects upon suppressed mitochondrial biogenesis and metabolic adaptability. Elevated GDF-15 provides additional support for mitochondrial stress and cellular injury. All of this goes to proving that AMI is indeed tightly linked in a network along which inflammation and metabolic dysfunction reinforce each other, fueling both myocardial and systemic responses towards a higher level of intensity [95].

Network Analysis of Cross-Omics Interactions

Via a cross-omics network analysis of the acute response to myocardial infarction, several densely connected molecular hubs were found, two of which are S100A8 and S100A9. These two nodes provide connection to protein abundance, mRNA expression and methylation-related inflammatory regulation. Also, these two nodes correlated with neutrophil proliferation, elevated IL-6 levels and metabolomic markers of cardiac ischemia and therefore support that calprotectin-mediated signaling is not only a marker of downstream inflammatory response, but rather an orchestrator of innate immune activation and metabolic disturbance [96].

The second major hub identified was IL-6 and its association with the expression of inflammation-based proteins, expression through transcriptomics and metabolism within the kynurenine pathway, which allows for the role of IL-6 to connect acute immune signaling to broader systemic effects, such as the synthesis of acute phase proteins, endothelial activation, and prediction of adverse clinical outcomes; high correlation of IL-6 to GDF-15 and CRP, as well as with long-term prognosis, further support IL-6 as an important mechanistic mediator and clinically relevant biomarker [97].

The identification of succinate as a metabolic hub is important in linking the disrupted TCA cycle to the inflammatory response. In addition to its role as a metabolic intermediate, succinate has been increasingly recognized as a signaling molecule that can stabilize HIF-1alpha and augment IL-1beta production. In the network as a whole, succinate serves as an important link between mitochondrial dysfunction and inflammation, providing a mechanistic pathway through which there is a strong association between metabolic demise and immune activation in AMI. Collectively, the findings of this network analysis highlight that the most informative biomarkers reside at the interface of multiple biological levels, and convey not only an association with disease but also ultimately play a role in the pathogenesis of that disease [98].

Temporal Dynamics Integration

Multi-omics-based approaches can provide a better understanding of molecular responses after the onset of cardiac symptom onset over time. When symptoms first begin (0-2 hours), neutrophil-derived proteins (e.g., S100A8, S100A9, myeloperoxidase [MPO], and lipocalin-2) were the primary markers, along with

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immediate early genes (i.e., FOS, JUN, and EGR family of transcription factors). These are part of an immediate stress-response program that begins to be activated prior to any significant troponin release (i.e., no potential for diagnosing heart failure in the initial moments) [99].

Cardiac molecular profiling demonstrated that between (2-6) hours after symptom onset, the major biological profile was more related to the systemic amplification of inflammation. There were both increases in acute phase proteins (e.g., CRP and serum amyloid A) and dominant levels of inflammatory cytokines (especially IL-6), with evidence of activation of the tryptophan–kynurenine pathway. This phase likely represents a continuum from localized ischemia to a systemic inflammatory state, during which both tissue damage related to ischemia and secondary injury due to immune activation become more intense [100].

Between (6-24) hours after the onset of symptoms, the molecular profile began to reflect increasing levels of repair and remodeling as evidenced by the increasing prominence of matrix remodeling proteins (particularly MMP-9 and TIMP-1), as well as elevation of growth factors (e.g., VEGF) and initiation of the production of anti-inflammatory mediators (e.g., IL-10 and TGF-β) associated with resolution and repair. The organization of the molecular markers according to time of response suggests that the interpretation of biomarkers should account for the phase of cardiac injury from which each biomarker is obtained, as the biological significance of many biomarkers depends on when they were sampled. This data implies that differences in treatment strategies may be required to address the distinct phases of an inflammatory (earliest cellular) response, amplified inflammatory (middle) response, and resolving/remodeling (latest cellular) response to cardiac injury[101].

Identification of Novel Therapeutic Targets

A key advantage of integrating multi-omics data is the capacity to identify mechanistic targets as opposed to just confirming biomarker presence. For example, the significant and consistent overexpression of S100A8/A9 at both the transcript and protein level makes it an attractive target as it lies at the nexus of inflammatory, neutrophil-driven networks and an excess inflammatory response after an AMI. In particular, calprotectin signaling has strong associations with early diagnosis and subsequent downstream cytokine activation. Consequently, it is plausible that blocking the signaling of calprotectin would lead to reductions in excessive innate immune activation following an AMI, particularly given the existence of preclinical development for monoclonal antibody strategies that could enhance translational potential [102].

GDF-15 is also an attractive target, particularly as a biological marker of mitochondrial stress and adverse prognosis following an AMI. Although GDF-15 may also have protective or compensatory roles, its strong correlation with infarct size and mortality suggests that modifications of upstream events that drive its release may effectively protect the heart from injury due to AMI [103].

The kynurenine pathway activated by IDO1 is another potentially accessible pathway for drug development. Activation of this pathway leading to immune dysfunction/immune dysregulation, endothelial dysfunction, and prolonged inflammation are likely contributors to metabolic coupling and inflammation occurring in high-risk patients. Thus, inhibiting IDO1 would provide a potentially valid adjunctive approach to treating metabolic-inflammation coupling after an AMI. Integrated data suggest that in the future, AMI treatment will involve combining reperfusion with targeted modulation of inflammation, metabolism, and mitochondrial stress [104].

11. Clinical Translation and Implementation

Proposed Diagnostic Algorithm

These finding, if confirmed in the clinical setting, support a new diagnostic algorithm whereby a multi-omics panel, consisting of proteins, metabolites, transcripts, methylation markers, and selected microRNAs, is obtained at the time of presentation and will generate a composite diagnostic score in 30 to 45 minutes. Triage decisions will be made much earlier during emergency department evaluation than they currently can be made using serial biomarkers.

Patients with very low scores would be classified as low probability for acute myocardial infarction (AMI), with the high negative predictive value of the score allowing for safe discharge from the emergency department or low-intensity observation with outpatient follow-up. Intermediate scores would identify patients who require continued monitoring, serial troponin measurements, and possibly additional imaging studies. High scores would provide a very high probability of AMI and indicate the need for rapid escalation to invasive or reperfusion therapy, especially when there is concordance with clinical symptoms and ECG findings [105].

While troponin and ECG testing would still continue to be performed, this diagnostic algorithm does not

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eliminate them but rather complements them. High sensitivity troponin will remain the confirmatory test in many circumstances at 1 to 3 hours; imaging studies will continue to provide functional and anatomical information. The use of a multi-omics panel will change the timing of ruling-in and ruling-out diagnosis, allowing for physicians to make those determinations much sooner than they currently do [106].

Comparison with Current Standard of Care

At present, serial troponin levels taken at the point of entry into the ED will not yield diagnostic confirmation unless serial troponins are taken at 0, 3, and in many instances 6 hours post-symptom presentation. These delays lead to prolonged ED observation while waiting for a definite diagnosis. The sensitivity for identifying troponin in the first few hours following symptoms remain limited; however with serial sampling sensitivity improves [107].

The multi-elementomics assay results in a greater sensitivity at the time of entry to the ED compared with serial troponin measurements and is returned in less than 60 min. Therefore it may provide a means to eliminate hours of diagnostic delays and facilitate early initiation of reperfusion, antithrombotic therapy, and/or safe and timely discharge when appropriate. This approach will also help to reduce overcrowding and improve flow within the ED, ultimately enhancing ED length of stay [108].

Cost-Effectiveness Analysis

Although multi-omics tests cost more per test than determination of individual biomarkers, economic modeling indicates that the overall strategy is highly favorable because of downstream savings: moderate costs per test are offset by less time spent in the emergency department and less admissions for evaluation on an avoid rule-out basis, as well as shortening of time to necessary decision making. Since the costs of prolonged emergency observation and inpatient monitoring are high, even a modest reduction in diagnostic time can yield substantial savings at the population scale [108].

Making those calculations on a large scale with many hundreds of presentations each year for chest pain, decreased emergency department utilization, and admissions for avoid rule-out evaluations yield very large savings to the health system. Because the strategy not only reduces costs but improves diagnostic performance, and potentially patient outcomes, it is not just cost effective but potentially dominant, both less costly and more effective than traditional approaches, which is a considerable barrier to adoption in developing health systems[101].

Implementation Barriers

Despite its potential, several hurdles will need to be overcome before routine use is a possibility. From a technical perspective, the biggest limitation is the efficient coalescence of multiple omics measurements into a single rapid point-of-care platform with a turnaround time of less than one hour. Analytical standardization, calibration, and quality control across the various types of biomarkers will be key [102].

The regulatory barriers will also be significant, as a combined multi-marker test will require ample demonstration of safety, reproducibility and clinical utility to receive approval. Certification and the clinical laboratory follow-up of test, and a system of reimbursement from payers will also need to be defined. Finally, widespread adoption will be aided by clinician trust, ease of integration into workflows, and simple clear rules for interpreting complex molecular information into actionable decisions [103].

12. Limitations and Future Directions

Study Limitations

There are certain caveats with regard to this work. While large and multi-center, discovery occurred in a particular subset of populations and requires validation in more racially, ethnically, and geographically diverse groups. Some clinically important sub-groups (women, younger patients, some NSTEMI presentations are relatively underrepresented). Not all the omics layers were sampled longitudinally in all patients, reducing resolution of some temporal dynamics. Finally, the current cost and complexity of multi-omics profiling is still high and poses challenges for immediate scalability [104].

Technical Challenges

Important technical challenges remain in applying this strategy to routine practice. No single instrument exists today that can measure proteins, metabolites, RNA species, and methylation markers all together in a clinically useful length of time. Integration of data from different sources is not simple either, since machine learning models will need to be retrained regularly as new data come in. Sample puffering is another issue, as many analytes - especially RNA and labile metabolites - get more and more degraded when not processed quickly [105].

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Future Directions

Point-of-Care Multi-Omics Device

Another priority is creating a device based on microfluidic cartridges capable of analysing selected proteins, metabolites, and nucleic acid from a constituent barely network headcapillary blood sample. This platform should report results within 30min, seamlessly integrate with electronic health records, and return a simple risk score for use by clinicians[106].

Artificial Intelligence Integration

Artificial intelligence will be needed for clinical implementation. Deep learning models able to integrate molecular data with ECG, imaging, symptoms and comorbidities might provide individualised risk estimates in real time, whilst allowing adaptation of thresholds to the specific demographic or disease context, aiding diagnosis in heterogeneous patient groups[107].

Therapeutic Targeting

Targeting Biological Therapeutics working in the opposite direction, it will be crucial to test whether the identified biological pathways derive targetable therapeutic targets. Neutralisation of S100A8/A9, modulation of the kynurenine pathway through IDO1 inhibition, attempting to lower succinate accumulation and/or normalize acylcarnitine metabolism etc all seem reasonable adjunctive candidates in biomarker driven high-risk patients requiring cardioprotection [108].

Global Health Applications

For the rest of the world, however, reduced minimal sets/mini panels of loci will be needed. Then further towards the other end of the spectrum protein-based assays on S100A8/A9, CRP, IL-6 could lead us to the divinely time devoid place. Then angled lateral flow assays and a hallmark gaining increased takeup telemedicine for sample collection, analysis in a ‘central’ facility, possibly allowing coverage for rural areas119].

Conclusions

Summary of Key Findings

We find that a 25-marker multi-omics panel demonstrates excellent diagnostic performance for AMI at presentation, clearly outperforms Troponin in the ultra-early window, accurately predict AMI status across validation cohorts and in clinically relevant sub-groups such as early presenters and people with diabetes, “said senior author Dr. Sparshatt. “Beyond diagnostic utility, many of our biomarkers including GDF-15, NT-proBNP, OPG and kynurenine provide strong prognostic capability for major adverse cardiovascular events and 1-year mortality. Mechanistically, our integrated data reveal neutrophil activation, kynurenine pathway engagement and mitochondrial dysfunction as the main drivers of AMI biology. Economic modelling then estimated major healthcare savings through faster Triage and reduced unnecessarily unnecessary admissions.

Clinical Implications

The key clinical consequence is that multi-omics testing might permit accurate rule-in and rule-out decisions at the moment of presentation, rather than at some later point hours later, facilitating faster reperfusion for the true AMI, more accurate risk stratification, and shorter emergency department stays. Beyond just diagnosis, the molecular profile might identify patients who will benefit from adjunctive targeted anti-inflammatory or metabolic therapies.

Research Priorities

Key priorities for future work lie in large prospective validations across different populations, point-of-care multi-omics devices, therapeutic trials modulating the newly identified mechanistic pathways, and real-world evaluations of health economics.

The Road Ahead

Our vision is one in which the model of precision cardiology four, five gathers together multi-omics data, ECG, imaging and clinical variables into one compact diagnostic and prognostic package with risk-stratified care, biomarker-guided intervention intensities inside, and true theragnostic paradigm all the biomarkers informing both diagnosis and therapy. If technological simplification continues, it may be possible to scale even this effort and achieve a global approach to early AMI detection.

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