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MINI REVIEW

Advancements and Challenges of AI-Based Tools as an Effective Personalized Medicine in the Future for the Early Diagnosis of Pulmonary Hypertension

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Abstract

Personalized medicine is the customizable approach to medical treatment and healthcare decisions for individual patients based on their unique genetic, environmental, and lifestyle factors. Integrating Artificial Intelligence (AI) into personalized medicine could improve this diagnostic trend. AI predictive models have shown significant promise in diagnosing Pulmonary Hypertension (PH). PH is a complex and often underdiagnosed condition associated with significant morbidity and mortality. Early diagnosis, accurate risk stratification, and personalized treatment are critical for improving patient outcomes in this rare disease. Our review primarily focuses on the currently available predictive AI models for the early detection of Pulmonary Hypertension (PH) using electronic health records. We also emphasize the importance of advanced AI tools integrating additional features, such as genomics. Specifically, we discuss the use of machine learning techniques, including both supervised and unsupervised approaches. Despite the potential of AI predictive tools to transform early detection of PH, challenges remain in effectively integrating them into clinical workflows and interpretation. These challenges arise from issues such as the availability of large, unintegrated datasets, unclear definitions of clustered data, a lack of external validation, and the ineffective use of unstructured data, such as clinicians' notes.

Abbreviations

AUC: Area Under the ROC Curve; AUROC: Area Under the Receiver Operating Characteristic Curve; CXR: Chest X-ray; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; SVM: Support Vector Machine; PAH: Pulmonary Arterial Hypertension; PH: Pulmonary Hypertension; ML: Machine Learning; HER: Electronic Health Record; CTEPH: Chronic Thromboembolic Pulmonary Hypertension.

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Introduction

The 2022 ESC/ERS guidelines redefine Pulmonary Hypertension (PH) as a Mean Pulmonary Arterial Pressure (mPAP) > 20 mmHg at rest, confirmed by Right Heart Catheterization (RHC). This updated threshold reflects normal hemodynamic values and prognostic relevance. For Pulmonary Arterial Hypertension (PAH), the diagnosis now requires Pulmonary Vascular Resistance (PVR) >2 Wood Units (WU) and Pulmonary Artery Wedge Pressure (PAWP) ≤ 15 mmHg, distinguishing it from other PH subtypes.

pH encompasses a spectrum of diseases with diverse etiologies, classified into five major groups based on clinical and hemodynamic features:

- Pulmonary Arterial Hypertension (PAH) - includes idiopathic, heritable, and associated forms (e.g., connective tissue disease, HIV).
- PH associated with left heart disease - previously termed "PH due to left heart disease."
- PH associated with lung diseases/hypoxia - chronic obstructive pulmonary disease and interstitial lung disease.
- Chronic Thromboembolic PH (CTEPH) - caused by pulmonary artery obstructions from unresolved thromboemboli.
- PH with unclear/multifactorial mechanisms

Despite advances in pharmacological therapies that target key pathobiological pathways, such as the nitric oxide, prostacyclin, and endothelin systems, long-term outcomes for many patients remain suboptimal. Recent advances in molecular biology, genomics, and clinical technology pave the way for a new era of personalized medicine in PH. This means integrating deep molecular phenotyping, biomarker profiling, and advanced imaging to classify patients better, predict disease progression, and select the most effective therapies [1].

Personalized medicine, also known as precision medicine, is an innovative approach to healthcare that caters medical decisions, treatments, and interventions to individual patients' unique genetic, molecular, and clinical characteristics [2]. This approach is particularly critical for rare diseases affecting fewer than 5 in 10,000 people but collectively impacting millions worldwide. Rare diseases often present diagnostic challenges due to their heterogeneity and limited prevalence, leading to delayed or missed diagnoses [3]. For these patients, personalized medicine can improve early diagnosis and, thus, their outcomes.

AI has emerged as a cornerstone for realizing the potential of personalized medicine [4]. By processing vast amounts of complex data- including genetic information, clinical metrics, imaging results, and patient-reported outcomes- AI enables healthcare providers to uncover patterns and insights that guide individualized care. AI can also analyze genomic data in rare diseases to identify disease-causing mutations or biomarkers, facilitating early diagnosis and targeted interventions. AI's predictive modelling capabilities also allow clinicians to dynamically anticipate disease progression and tailor treatment plans based on real-time patient data [5]. Furthermore, AI-powered tools can stratify patients into subgroups with shared characteristics, enabling more precise treatment strategies for heterogeneous conditions [6]. AI's integration into personalized medicine has already demonstrated significant success across various medical domains. By analyzing multi-omics datasets and clinical records, AI can improve the accuracy and speed of diagnosing rare diseases [7]. This review focuses on studies involving the utilization of machine learning for the early detection of PH. To better understand AI's impact on PH, it is essential to examine the specific mathematical and statistical methods that underpin these advances. The following section briefly overviews the leading AI approaches in recent PH research, highlighting their methodological foundations and practical applications.

Brief overview of mathematical methods used in the surveyed papers

Machine learning can be divided into several categories. Two important ones used in the surveyed papers are unsupervised and supervised learning. Unsupervised learning can be used to detect patterns and groups in data without using labels. Clustering is a prominent example. Supervised learning uses labels and learning rules to learn hypotheses from the data. Well-known techniques relate to regression and classification. In classification, deep learning-based techniques have been proven useful [8].

Short survey on network-based approaches towards pulmonary hypertension

Networks or graphs are structural objects that are

nowadays ubiquitous [9]. Network-based approaches have been studied extensively in various disciplines, e.g., Network Medicine, Network Biology, Chemistry, Computer Science, Transportation, and so forth [10,11]. Particularly in medicine and related areas, network-based methods have been proven fruitful and efficient when solving problems in personalized medicine [10]. Note that several types of graphs exist in the mathematical literature, e.g., unlabeled, labeled, and weighted graphs [9]. Another aspect of graphs/networks relates to their structure, e.g., they can be cyclic, acyclic, and connected, they can possess so-called modules and other interesting subgraphs [10,11].

In this survey, we briefly review some important network-based approaches when investigating pulmonary hypertension [12] analyzed so-called modules of special networks in the context of pulmonary hypertension and performed a classification problem using random forest and other techniques [12]. Employed network medicine to identify 21 patient subgroups ("modules") using 79 clinical variables. This work highlights pulmonary arterial compliance potential as a prognostic biomarker and suggests its integration into PH diagnostic criteria.

The next work by Zang H, et al. [13], systematically mapped non-coding RNA (ncRNA) networks driving pulmonary vascular remodeling [13]. Notably, ncRNAs show promise as both diagnostic biomarkers and therapeutic targets for reversing vascular remodeling.

Another example from Liu M, et al. [14] applied network centrality measures to PH patient outcomes. This analysis provides a framework for targeting specific psychosocial factors in PH management. By combining these approaches, researchers can develop personalized strategies targeting both biological mechanisms and quality-of-life determinants in pH [15]. The quality of life and fear of progression in the context of pulmonary hypertension can be estimated using network centrality; this concept is an important tool to determine the 'importance' of vertices in a network [11].

Machine learning (ML) for PH detection using Electronic Health Record (EHR) data

One study using a patient-level US-based EHR database indicates that ML can favour PH detection without additional examination or personal visits to the clinic [16]. This model utilized 165 features, including demographics, diagnoses, procedures, prescriptions, and laboratory results, and reached excellent performance for PH detection - AUROC 0.92. Interestingly, this prediction was calculated 18 months before confirmation of diagnosis, with AUROC ranging from 0.79 to 0.96 for subgroups like Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH). The most predictive features were heart failure, shortness of breath, and atrial fibrillation. Does this approach promise to reduce diagnostic delays and improve patient outcomes by leveraging existing EHR data without additional testing?

The 'most predictive features' cited in the study are not exclusive to Pulmonary Hypertension (PH). They may arise, for instance, in contexts of acute left ventricular heart failure or paroxysmal atrial fibrillation. The findings from the study may significantly depend on the patient's hemodynamic status and compliance during clinical data collection. Additionally, the term 'PH symptom' may be misleading, as it could equally represent symptoms associated with heart failure. Given that Left Heart Disease (LHD) is recognized as the predominant etiology for pH [17], the study fails to clarify whether participants received optimal heart failure management or if underlying heart failure etiologies were considered. Consequently, it is challenging to ascertain whether the reported 'PH symptoms' were exclusively manifestations of left-sided heart failure.

Secondly, the study lacks external validation in diverse populations or healthcare settings, which is pivotal for evaluating the robustness and generalizability of Deep Learning (DL) models. Adequate external validation necessitates testing a finalized model on an independent dataset excluded from model development or internal validation phases. This step mitigates the risk of over-optimistic performance assessments from overfitting or dataset-specific biases. The absence of this validation raises questions about the applicability of findings to non-U.S. or under-resourced healthcare environments. Moreover, reliance on a de-identified EHR database may introduce additional biases due to inconsistent or incomplete data documentation in real-world scenarios [18]. To enhance interpretability and transparency in predictions, employing AI-driven clinical language models trained on authentic clinical narratives and SHAP (Shapley Additive Explanations) for interpretation may prove advantageous [19]. A multi-institutional strategy may strengthen the

study, incorporating extensive datasets, single-centre recruitment, retrospective cohort analyses, and training datasets from various international contexts [20].

Thirdly, while the performance of subgroups such as PAH and CTEPH was assessed, other PH subtypes may have been overlooked, potentially masking variations in predictive accuracy across diverse PH etiologies. The underlying causes of PH are critical determinants of diagnosis, disease trajectory, and clinical presentation. Therefore, individual AI tools tailored to each pH type and underlying etiology should be considered, because each patient is different and may present with distinct clinical features.

Furthermore, diagnosing PH requires both echocardiography and right heart catheterization; these two modalities serve complementary roles and should not be directly compared when used in isolation. Echocardiography is the primary non-invasive screening tool for pH. It estimates pulmonary artery pressures and assesses right heart function, providing an initial indication of the disease. Right heart catheterization is the gold standard for confirming the diagnosis of PH. It directly measures pressures in the pulmonary arteries and right heart chambers, providing definitive and quantitative data.

Moreover, with 165 features in a relatively narrow dataset, the study faces a substantial risk of overfitting, particularly in the absence of detailed disclosures regarding regularization techniques or feature selection methodologies employed during model training. Translating this model into clinical practice will encounter obstacles such as interoperability challenges across EHR systems and the necessity for infrastructure to facilitate real-time predictions. Ethically, employing machine learning models in healthcare introduces concerns surrounding transparency and potential prediction biases. For instance, if demographic data utilized during model training is not managed carefully, it may perpetuate disparities in healthcare access and outcomes. Although the study presents performance metrics, it lacks a comprehensive comparison with other machine learning-based diagnostic models for pH.

Machine learning (ML) for PH detection using EHR data and proteomics

The study by Sweatt AJ, et al. [21] explores the use of machine learning and precision medicine to identify immune phenotypes in Pulmonary Arterial Hypertension (PAH). The primary aim of this study was to identify distinct immune phenotypes in patients with PAH using unsupervised machine learning (here: clustering) analysis of blood proteomic profiles. Specifically, the study sought to classify PAH patients based on circulating cytokine, chemokine, and growth factor levels to uncover potential heterogeneity in inflammation. This could help select enriched clinical trial cohorts, potentially increasing the efficacy of therapies by targeting specific patient subgroups.

The study highlights significant advancements in refining patient subgroups through clinical data and immune profiling. However, the findings indicate that clinical data alone may not predict PAH adequately. Consequently, incorporating genomic and molecular data is likely necessary for more precise prediction and classification. Additionally, the study does not address the evolution of immune phenotypes, which is vital for understanding disease progression and the potential effects of therapeutic interventions. While implementing an unbiased machine learning approach is innovative, it could benefit from further external validation with independent datasets to enhance its robustness.

Utilizing unsupervised machine learning, specifically consensus clustering, to examine PAH offers valuable insights into immune-based phenotypes. However, this approach presents methodological and interpretative challenges. Consensus clustering may create a false sense of stability in the data if it lacks biologically meaningful subgroups. Although the study identified four immune phenotypes with distinct cytokine profiles, the weak separation between clusters—illustrated by continuous gradients of inflammation—might lead to misleading results. Simulations have demonstrated that unimodal data can yield seemingly stable clusters [22]. Given PAH's heterogeneous nature and overlapping inflammatory patterns, this could result in the misclassification of patients and affect therapeutic decisions. Overall, while the validation strategy in the PAH immune phenotyping study shows reproducibility across populations, it faces significant challenges inherent in the consensus clustering methodology. Table 1 compares the validation and discovery cohorts.

Furthermore, determining the optimal number of clusters (in this case, K = 4) presents ongoing

Table 1: Comparison of cohorts.

Factor	Discovery Cohort	Validation Cohort
Assessment of symptoms	6-minute walk test	Incremental shuttle walk
Comorbidity data	Available	Unavailable
Outcome definition	Transplant-free survival	Death only

challenges. Although the PAC method (Proportion of Ambiguous Clustering) was employed to assess stability, alternative metrics such as the original Delta-K approach are susceptible to errors. This raises concerns regarding reproducibility, particularly with small sample sizes or dynamic inflammatory profiles over time. It is crucial to note that the study is based on blood cytokine profiles, which may be influenced by measurement errors, batch effects, or uncontrolled confounders (such as medications). Unsupervised methods can exacerbate this noise due to the absence of external labels for correction [20]. Moreover, the choices made during pre-processing (for example, normalization techniques) can substantially impact cluster formation. The identified cytokine networks could theoretically serve as potential therapeutic targets. However, the stability of these clusters over the disease course or their variability under treatment remains uncertain. The presence of non-stationary data (such as changing inflammatory patterns) diminishes the generalizability of the models.

While the study achieved technical reproducibility, broader validation and adaptations should be taken into consideration [20]:

- External cohorts with alternative clustering pipelines
- Dynamic profiling to assess phenotype stability
- Biological experiments confirming cluster-specific mechanisms
- Algorithm-agnostic validation using metrics like ARI (Adjusted Rand Index)

As highlighted in clustering validation frameworks, consensus results remain provisional until confirmed through multidisciplinary integration of computational, clinical, and experimental evidence.

To better understand, we present a comparison table 2 summarizing the studies explicitly mentioned and discussed in our article, focusing on their methods, performance, and validation strategies for AI-based PH prediction.

Future Directions

The integration of AI with EHRs, Electrocardiograms (ECGs), echocardiograms, and imaging data offers promising avenues for improving the early detection and management of PH (DuBrock HM, et al. [6], Fadilah

Table 2: Comparison of the studies' AI-based PH prediction tools.

Study (Year) & Reference	Data/Modality	AI/ML Method(s)	Performance Metrics	Validation Strategy	Key Findings/Notes
Leha A, et al. [25]	Echocardiography (90 patients)	Random Forest, SVM, Lasso Regression, Boosted Trees	AUC: 0.78-0.87 (various models); Random Forest Regression: AUC 0.87 (95% CI 0.78-0.96)	10 x 3-fold cross-validation	ML models predicted PH with high accuracy using multiple echo features, outperforming formula-based approaches.
Fadilah A, et al. [23]	Meta-analysis (Echocardiography, CXR, CT, MRI, biomarkers)	Various ML algorithms (meta-analysis)	Echocardiography: Sensitivity 0.83, Specificity 0.93; Pooled: Sensitivity 0.82, Specificity 0.82	Random-effects meta-analysis, subgroup analysis	ML methods show high diagnostic accuracy, especially with echo data; heterogeneity noted across modalities.
Kogan E, et al. [16]	Electronic Health Records (EHR), US-based	Gradient Boosting (XGBoost)	AUROC: 0.92 (overall); Subgroups: PAH 0.79-0.90, CTEPH 0.87-0.96	Train/test split (90/10%), subgroup analysis	ML model identified PH up to 18 months prior to diagnosis using 165 EHR features; most predictive features included heart failure, shortness of breath, and atrial fibrillation.
Sweatt AJ, et al. [21]	Blood proteomics (PAH patients)	Unsupervised ML (Consensus Clustering)	Four immune phenotypes identified; technical reproducibility	Discovery and validation cohorts	Identified immune subtypes in PAH; clinical data alone is insufficient, so multi-omics integration is needed.
Wang, et al. 2023 [12]	Multi-omics, network data	Network-based ML (Random Forest, Modules)	Not specified (classification focus)	Not detailed	Network analysis of RNA interactions for PH subtyping; highlights value of network-based approaches.

A, et al. [23], Kwon J, et al. [24], Leha A, et al. [25]) demonstrated that machine learning models outperform traditional formula-based approaches in predicting PH using echocardiographic data. This work supports ML as a superior alternative to formula-based PH prediction, particularly in variable echocardiographic data quality settings. These advancements offer significant opportunities for future companies to develop innovative AI solutions for screening in each type of PH using all available modalities. Potential business models include the development of AI-enhanced medical devices like portable imaging tools that integrate clinical, genetic, and analytic blood sample data for point-of-care diagnostics. Using the clinical language model or Natural Language Processing (NLP), AI models can be beneficial in analyzing and extracting information from unstructured data such as clinician notes [19].

Conclusion

Advancements in AI provide partial solutions to the limitations of consensus clustering by allowing for multimodal validation and ongoing monitoring. Additionally, structural network analysis proves to be effective when studying pulmonary hypertension. However, these methods do not resolve fundamental issues such as the subjective nature of cluster definitions and the challenge of biological interpretability. Using AI to test clustering hypotheses instead of replacing them, a combined approach could enhance translational relevance while reducing the risks of overinterpretation [26]. Finally, integrating multi-omics and imaging data with AI in individual PH groups can provide insights from various health settings, thereby strengthening and validating the efficacy of the studies [27].

Author Contribution

Research AM, GA, & MD; Writing AM, GA, MD; Reviewing & Editing GA, AM, & MD.

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Conflict of Interest

The authors declare no conflicts of interest.

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