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REVIEW PAPER

Precision Medicine in Emergency Medicine

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Abstract

Personalized medicine was always a part of medicine. However, with technological advances in data mining, machine learning, artificial intelligence and computing, the term "personalized" has been surpassed by precision medicine, a multidisciplinary bridge that aims to provide unique approaches for each patient. Acute care is an area where current precision medicine methods is starting to transform. In this mini review, we describe in brief some of the applications used in emergencies that promote precision medicine.

Keywords: precision medicine, emergency medicine, artificial intelligence, acute care

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1. Introduction

The industrial revolution of automation, robotics and data exchange techniques has transformed to its fourth version. Healthcare has also been driven to refine the quality of diagnosis and therapy through artificial intelligence (AI) and robotics penetration. Thus Industry 4.0 has resulted in Healthcare 4.0. Precision medicine is one of the main results of Healthcare 4.0 (along with AI, connected care and smart medicine) [1]. Digital health advancement has been an important booster for precision medicine progress. Wide application of personal mobile technologies (the "mHealth" trend), wide implementation of electronic health records, information technology progresses in data storage and analysis capabilities along with wider public computer and health literacy have contributed in various degrees to that progress.

This paper is focusing on precision medicine applications in emergency medicine and critical care.

2. Terminology

According to Precision Medicine Cohort Program, "Precision medicine is an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle. Precision medicine seeks to redefine our understanding of disease onset and progression, treatment response, and health outcomes through the more precise measurement of molecular, environmental, and behavioural factors that contribute to health and disease. This understanding will lead to more accurate diagnoses, more rational disease prevention strategies, better treatment selection, and the development of novel therapies. Coincident with advancing the science of medicine is a changing culture of medical practice and medical research that engages individuals as active partners—not just as patients or research subjects" [2].

Though the concept is not new, it was until the last 15 years that precision medicine applications and interest increased. Prior to 2007, there are about 4000 related publications in National Library of Medicine, PubMed® database, while after 2007, the number climbs to the astonishing 73.000 publications [3, 4]. During this time, there has been a change in terminology use. "Precision medicine" has surpassed the older terms "personalised" and "targeted" medicine, which are now considered misleading, since medical practice per se should be adapted and aimed at the individual patient. Medicine should also be precise, yet the currently accepted terminology, implies better understanding of individual data will lead to more optimised treatment and outcome. It seems that precision medicine is a process that incorporate stratification of patients (i.e., stratified medicine), detailed phenotyping data analysis and targeted therapy [3, 4].

3. Precision medicine in various areas of emergency medicine

Though in other areas, like oncology, precision medicine applications have become more popular, the unique characteristics of emergency medicine and especially pre-hospital care (mainly time and resources limitation) create additional difficulties. In the latter field technology with machine learning (ML), artificial intelligence (AI) and big data analytics offer tremendous help.

3.1. Medical imaging

In medical imaging, application of information and communication technologies for healthcare services have triggered the growth of medical imaging informatics [5], defined by the Society for Imaging Informatics in Medicine (SIIM) as "touches every aspect of the imaging chain from image creation and acquisition, to image distribution and management, to image storage and retrieval, to image processing, analysis and understanding, to image visualization and data navigation; to image interpretation, reporting and communication" [6]. Similar to genomics and proteomics, "radiomics" combine medical imaging with clinical and laboratory data towards advancing precision medicine.

A practical example of that evolution in emergency medicine is to reform the widest imaging field, point-of-care ultrasound (POCUS) as help guide not only to image acquisition but also to clinical decision-making [7]. The latter extends beyond clinical algorithms to 3D image reconstruction and in silico modelling. Thus, for example clinical and monitoring input data from cardiac ultrasound could provide personalized diagnosis and prediction models in order to optimize intervention choices. This can minimise operator dependence in the use of POCUS and can be extremely valuable both as a field tool- especially in remote or austere condition, or in a mass casualty incident. Good results have been also published in its use for vessel identification and fluid prediction responsiveness via pattern recognition and quantitative measurement (e.g. inferior vena cava ultrasound) [8, 9]. Transfer of data capabilities and remote consulting augment the safety and the efficacy of healthcare intervention. Moreover, it seems that the future could be combination of the previous ones for comparison from previous data from the same patient or from a database of other patients with similar findings/conditions in real time.

3.2. Triage

Emergency triage and priority systems is another field that AI revolutionises. Triage, i.e. identification and stratification, becomes particularly challenging especially for the patients who are far from hospital and use telemedicine system [10]. Research on the topic is not new with various kind of focus—from forecasting models for Emergency Department (ED) revisits to triaging anaphylaxis [7]. Such triage system has also been proposed for paediatric populations with good results [11], or for prioritising those patients in ED that will probably need admission to Intensive care Unit (ICU) [12].

Other models using machine learning and natural language processing have been tested in identifying critical patients presenting to the emergency department with risk of mortality and cardiopulmonary arrest [13]. In a recent meta-analysis about AI use in predicting cardiac arrest, AI-Early Warning Systems outperformed traditional warning systems (Early Warning Score, Modified Early Warning Score, National Early Warning Score and Paediatric Early Warning Score) in 9 out 10 studies included in the review [14]. Natural language processing have been also used for improving diagnosis of diseases and conditions that are difficult to identify by clinical gestalt only, such as anorexia nervosa, aneurysms, coronary artery disease or Kawasaki disease [8, 15]. Other machine learning models have been tested for prediction of hospital's practice to perform coronary angiography in adult patients after out-of-hospital-cardiac-arrest and subsequent neurologic outcomes, with promising results [16].

The COVID-19 pandemic has posed new challenges for the healthcare systems. Digitally automated pre-hospital triage via AI systems has been proposed as an alternative for better healthcare supply and demand matching [17].

3.3. ARDS

Contribution of precision medicine methods to COVID-19 pandemic has not been limited to emergency triage and priority systems. Acute Respiratory Distress Syndrome (ARDS) is an umbrella term, a heterogenous clinical syndrome. Though the heterogeneity of ARDS was long known before SARS-Cov2 appearance, COVID-19 pandemic triggered even more the interest about different subphenotypes. The latter needs different therapeutic strategy approaches; the earlier the therapy is applied, the better the outcome [18]. Today, hypoxaemia stratification by Berlin criteria seems inadequate, and ARDS wider "space" is better reorganizing into smaller "parts" depending on cause, anatomic distribution respiratory mechanics, inflammatory response patient's age, proteomics, metabolic or genetic factors [19]. Furthermore, the subset of observable characteristics (subphenotype) can be a result of one or more distinct biology (also referred as endotypes) and critically ill patients transition or combination of subphenotypes may exist. Progress can be achieved at many levels: preclinical modelling can replicate ARDS heterogeneity and enable better understanding of pathophysiological key nodes in every endotype in each phase of the disease; thus providing us with possible biological drivers for therapeutic targeting. At clinical level, large observational cohort studies could include large sample sizes to ensure statistical power for dissecting clinically occult heterogeneity; could improve prognostic and diagnostic capabilities and serve as a guide for the choice of the optimal available therapy [20]. Lessons and experience gained from COVID-19 pandemic, like the introduction of big platfoms trials, such as RECOVERY, I-SPY2, PreCISE and more others, are expected to change the future ARDS landscape.

3.4. COPD

Emergency medical molecular phenotyping analyses (e.g., genomics, transcriptomics, proteomics, and metabolomics) could be a way of phenotyping not only ARDS, but also other conditions and diseases, such as asthma, chronic obstructive respiratory diseases (COPD), or sepsis [3]. In COPD, the use of different type of biomarkers (predictive-used for identifying patients' subgroups, response-used for evaluation of a therapy effectiveness, prognostic-used for forecasting possible poor outcome) are essential part of precision medicine.

Examples of such biomarkers are serum concentration of a-1 antitrypsin (response), BODE (body mass index, air flow obstruction, dyspnoea and exercise) index (predictive) or blood Eosinophil count (predictive biomarker in determining therapeutic guidance for inhaled corticosteroid therapy) [21]. Hence, apart from the old and widely accepted phenotypes of chronic bronchitic, emphysematous, asthma-COPD overlap, frequent and rare exacerbator; new phenotypes are emerging: pulmonary cachexia, overlap COPD and brochiectasis, upper lobe-predominant emphysema, the fast decliner and the comorbidities (or systemic) phenotype [22]. The latter could demystifying some findings from evidence-based data: such as why most COPD patients do not benefit from ICS therapy, or when to administer anti Ig-E therapy, or why there is tremendous variability in the background rate of exacerbations across patients included in the Macrolide Azithromycin for Prevention of Exacerbations of COPD (MACRO) study and create new therapeutic protocols.

3.5. Sepsis

Sepsis is a heterogeneous condition including various clinical courses and numerous endotypes and subphenotypes. Examples of that diversity are unique phenotypes of thrombocytopenia-associated multiple organ failure (TAMOF), sequential multiple organ dysfunction (SMOF), immunoparalysis, or macrophageactivation syndrome (MAS). Each of them needs different therapeutic approach [23]. Research is being carried out in several directions: bioinformatics and genomyics (genomics, metabolomic, transcriptomic, proteomic) data analysis along individualised therapies (immunoglobulins, endotoxic and cytokine hemadsorption, immunoparalysis) and the landscape of sepsis is to be changed drastically in the future [24]. Several genetic variants that may contribute to immunocompromised state and poor outcomes have been identified: Toll-like Receptor 1 variant, Sepsis Response Signature 1 genetic profile, Complement component 2 (C2) polymorphism, β_2 adrenergic receptor genetic polymorphism and Human leukocyte antigen (HLA) variations are some of them [24]. Early detection of those variants can lead to optimisation of therapy and outcome improvement.

3.6. Trauma

Precision medicine methods have been also used and evaluated in several trauma conditions. The Uniformed Services University Surgical Critical Care Initiative (SC2i) was established in 2013 to develop Clinical Decision Support Tools (CDSTs) for acute trauma care. With more than 1600 enrolled patients and 20 million data elements, SC2i has already released CDSTs for activation of massive transfusion protocol and CDSTs for extremity wound management and venous thromboembolism therapy are under way. Other CDSTs are about prediction of the onset of sepsis, and the prediction of the development of invasive fungal infections, bacteraemia and pneumonia [25].

Other examples include research about the “early appropriate care” in pelvis and femur fractures, which identifies the patients that will benefit from early definitive fixation; and how interventions affect individualized immunologic response. The latter could be used for prognostic modelling and for identification of subgroups with surgically induced “second-hit” inflammatory response [26]. Promising results are also reported from studies using peripheral blood special biomarkers after orthopaedic trauma in predicting fracture healing in a personalized, patient-specific manner. There are studies that have shown that single transcriptomic metric of blood leukocyte gene expression can be used in blunt trauma cohorts at 24 h to distinguish patients who rapidly recover from those with complicated clinical trajectories. The latter genomic score is based on a set of 63 blood leukocyte genes (S163) performed using NanoString technology [27].

In trauma brain injury (TBI), identification of particular genomic and epigenomic predispositions could improve overall outcomes. There are more than 33 TBI genes that have been associated with various outcomes, such as apolipoprotein E (Apo E) allele, interleukin 1β variant or certain angiotensin-converting enzyme (ACE) receptors subtypes. They generally fall into two groups: response to injury and neurocognitive reserve; and their role in TBI is expected to change future management [28].

3.7. Stroke

Stroke is another umbrella condition including a variety of cerebrovascular conditions. Precision medicine research promises early differentiation of ischaemic stroke from acute non-stroke pathologies (e.g. myocardial infarction and epilepsy), as well as intracranial haemorrhage and transient ischaemic attack. Moreover, it can now identify special treatment options for certain conditions, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) or Fabry disease (FD) and forecast possible outcome is certain patients group via biomarkers’ and neuroimaging data analysis [29]. Moreover, stroke is highly dynamic process. Penumbra (the area surrounding the initial infarct area-the core-) is the therapeutic target in acute stroke management. Yet, the speed of the penumbra-core transformation varies greatly and is highly subjective: some do have any penumbra (i.e. salvageable brain tissue) few hours after stroke while in others it can be found up to 17 h after the incident [30]. Precision medicine uses mathematical techniques and data analysis to provide individualized predictions for patients and differentiation of pathology patterns [31]. Current research utilizes model simulation-based approach which allows calculation of cerebral hemodynamics based on the patient-individual vessel configuration derived from brain vascular imaging [32], thus, identifying possible therapeutic targets in individual cases.

3.8. Geographical information systems

Among multiple possibilities of the modern technology is the geospatial AI (also known as GeoAI), which combines geographical information systems' methods, AI, data mining along with EHR, personal mobile health sensors to create new approaches and datasets in EM. Thus, it can facilitate creation of cost-effective solutions to tackle challenges regarding access to emergency services, restructuring of healthcare networks, creation of catchment areas, estimation of population coverage using satellite imagery, identification of mobility patterns, and identification of risk areas for specific health events in terms of their characteristics [4, 33]. A recent study tested seven machine learning algorithms for real-time routing model and proposed EMS vehicle routing at the time of emergency, considering partial outsourcing [34], while several other studies have accessed both population characteristics and resources distribution. Hence, GeoAI can help not only in improving precision medicine (better/earlier identification of individual in special needs and better allocation of the necessary care) but also augment what is called "precision public health". The latter, though not yet totally defined, may simply seen as application of precision medicine to many [35].

3.9. Other

In paediatrics, such analyses could contribute to rapid screening for any genetic or cancer diseases [35]. Recent advances of cell-free DNA diagnostics facilitate more accurate decision for inflammatory diseases, stroke, and cancers [36]. The overall impact is already visible: in a recent large study, almost 20% of US ED visits involve a medication with a pharmacogenetic recommendation that may impact the efficacy and toxicity for individual patients [37]. Other projects, like the Emergency Medicine Specimen Bank (EMSB): a biorepository of clinical health data and biospecimens collected from all adults who are able and willing to provide consent and are treated at the University of Colorado Hospital Emergency Department, or the Lifelog Bigdata Platform (a big data cloud system), could also facilitate precision medicine in acute care [38, 39].

3.10. Conclusion

Challenges remain as the aforementioned are far from wide application. However, their importance is accepted by everyone, both healthcare providers and healthcare users. Precision medicine methods can change every aspect for healthcare: individual approach to the one who needs it, precision public health, precision medical education along with education about precision medicine, and healthcare systems. It appears that once again, human factor and our ethics will be the cornerstone for their global use: as long as we do not forget the purpose of medicine and caring, the future seems very promising.

Data availability

No datasets were generated or analyzed during the current study.

Conflict of interest

The author has no conflicts of interest to declare.

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