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Artificial intelligence, precision medicne, and fracture-related infection: Concepts and framework

Oluwasegun A Aremu[1*], Oluwatomisin F Ogunlade[2]
[1] Department of Surgery, College of Medicine, University of Ibadan, Ibadan, Nigeria
[2] Department of Orthopaedics and Trauma, University College Hospital, Ibadan, Nigeria

Abstract

Fracture-related infection (FRI) constitutes a major sequela of orthopaedic trauma care that remains a burden both to the patient and the orthopaedic surgeon. The recommendations by the FRI consensus group serve as a guideline for FRI management, the diagnosis and management of FRI continue to evolve. The general management principles of FRI are multidisciplinary approach (MDT), host optimization, adequate debridement, soft tissue management, dead space management, bone defect management, appropriate use of local and systemic antibiotics, and early rehabilitation. In the era of precision medicine and artificial intelligence, however, it is possible to provide a targeted care to patients with FRI in view of the available surgical options.

There are two major surgical concepts in the management of FRI. The surgical decision depends on several factors which include fracture stability, extent of soft tissue compromise, host factors, causative pathogens, intramedullary nature of implants, and time frame since onset of symptoms. One major limitation of the current surgical approach to the management of FRI is that the decision is dependent on the state of biofilm formation, which is time-dependent. Another major limitation is lack of a clear guideline on which patient benefits from a single-stage surgery or multi-stage surgeries.

With the rise of precision medicine in clinical practice, coupled with the recent evidence of individualized treatment of FRI, it is possible that the management of FRI could become a targeted therapy. Artificial intelligence has made the objectives of precision medicine possible. This will involve integration of multiple data sources using artificial intelligence, and developing a model that is internally and externally validated. Though there will be challenges to the realization of this feat, those challenges are not insurmountable.

Keywords: Precision medicine, artificial intelligence, machine learning, fracture-related infection, framework

Introduction

Fracture-related infection (FRI) constitutes a major sequela of orthopaedic trauma care that remains a burden both to the patient and the orthopaedic surgeon [1]. FRI has been a major topic of discussion in the literature [2]. and considering its prevalence, societal burden, associated morbidities, and cost of treatment [3]., it remains an actively researched area [4, 5].

While the recommendations by the FRI consensus group serve as a guideline for FRI management, the diagnosis and management of FRI continue to evolve. Though the confirmatory criteria for diagnosing FRI are clear, the suggestive criteria and the low predictive values of the inflammatory markers, coupled with the limited availability of advanced imaging, opens up a diagnostic challenge [6]. The importance of establishing a diagnosis cannot be over-emphasized, as this usually informs the management strategies and guidelines to follow. Whether the diagnosis of FRI is confirmatory or suggestive, the general management principles are the same: multidisciplinary approach (MDT), host optimization, adequate debridement, soft tissue management, dead space management, bone defect management, appropriate use of local and systemic antibiotics, and early rehabilitation [1]. In the era of precision medicine and artificial intelligence, however, it is possible to provide a targeted care to patients with FRI in view of the available surgical options.

Surgical Management of Fri: Overview

There are two major surgical concepts in the management of FRI: (1) debridement, antimicrobial therapy, and implant retention (DAIR) (2) debridement, antimicrobial therapy, and implant removal if the fracture has healed, or implant exchange if the fracture has not healed. These two major surgical concepts are combined with the general management principles earlier mentioned [1]. The surgical decision depends on several factors which include fracture stability, extent of soft tissue compromise, host factors, causative pathogens, intramedullary nature of implants, and time frame since onset of symptoms [7]. Implant retention is usually recommended in the presence of stable osteosynthesis, normal host, adequate soft tissue cover, possibility of adequate debridement, and a short interval from onset of symptoms. The recommendation is implant removal or exchange in the presence of unstable fixation, unacceptable reduction, poor host physiology, extensive infection, and prolonged onset of symptoms [8]. Any of the surgical options can then be combined with other modalities like tissue sampling, antibiotic suppression, dead space management and local antibiotic therapy.

Limitations of Current Management Principles

One thing that is evident from the literature is that the decision to do DAIR or otherwise is closely related to the formation and maturation of biofilm, which is inherently time-dependent [9]. FRI occurring in the immediate post-operative period is usually due to early immature biofilm which can sometimes be susceptible to antimicrobials, and this may explain why the DAIR surgical approach is usually followed in such situations, since the fracture stability after fixation is usually not compromised at that time. As the post-operative period progresses and the biofilm evolves into a mature one, it becomes difficult for antibiotics to penetrate the maturing biofilm. This leads to progression of the infective process, compromised fixation, and subsequent instability [10]. Recent evidence, however, suggests that not all patients will benefit from DAIR, even if the FRI is early [11]. There are also no clear guidelines to decide whether a patient will benefit from a single-stage implant exchange or a multi-stage implant exchange [12]. What is becoming apparent is that each FRI case is different, and it will require a personalized approach to achieve the best optimal outcome. This was unequivocally demonstrated by Rupp M *et al* [13]. They were able to demonstrate in their study that using an individualized treatment approach for the management of FRI, through a multidisciplinary treatment (MDT), resulted in a better outcome.

Precision Medicine

According to The US National Human Genome Research Institute "Precision medicine (generally considered analogous to personalized medicine or individualized medicine) is an innovative approach that uses information about an individual's genomic, environmental, and lifestyle information to guide decisions related to their medical management. The goal of precision medicine is to provide a more precise approach for the prevention, diagnosis, and treatment of disease." [14]. While the term is not strange to the scientific community, the renewed interest in the concept can be attributed to President Barrack Obama, during his state of the union address in 2015, when he launched the Precision Medicine Initiative [15]. The initial focus of precision medicine was on cancer therapy, but the concept is now applied to diverse areas of medicine [15]. Also, genomic data alone was thought sufficient to answer the objectives of precision medicine. It is however clear now that social factors, environmental factors, and data from other biological processes are equally important [16].

The main objective of precision medicine is to use a patient's genetic profile, biological data, social, behavioural and environmental factors for selective targeted therapy. This usually involve processing of a huge amount of data, which hitherto was challenging and cumbersome. With the era of big data, artificial intelligence and machine learning, however, the prospect of achieving precision medicine is now a reality than ever [16].

Artificial Intelligence and Machine Learning

Artificial intelligence (AI) is a term that generally describe the use of computer machines to replicate intelligent behaviour without direct human intervention. While AI applications have gradually progressed over the years, the branches of AI that have been mostly applied to precision medicine is machine learning (ML) and deep learning (DL) [17]. ML can integrate multi-dimensional data such as genomic data, Electronic health records (EHR), biological data, social and behavioural data to facilitate precise and predictive healthcare solutions, which are the main objectives of precision medicine. The ability of ML and DL to learn intricate pattern from multiple high dimensional data sources, and find the interrelationship between these multiple data elements to define personalized care, makes them invaluable tools in achieving the goals of precision medicine [18, 19] One field of medicine that has seen rapid progress in the application of AI to achieving individualized care is precision oncology [20]. Though still nascent, there have been recent advances targeting precision medicine in some aspect of orthopaedics. There is a recent shift towards precision medicine in the management of osteoarthritis through integration of regenerative medicine, stem cell therapies, gene therapies combined with use of innovative biomaterials, circadian biology, and organelle health [21]. Similar advances have also been made in the management of rheumatoid arthritis [22]. and musculoskeletal tumours [23]. There are few studies that have discussed how advanced molecular diagnostic tests and radiomics can be used to achieved precision medicine in the management of musculoskeletal infection [24]. These studies however did not fully assess the wide range of multi-dimensional data available for achieving precision medicine. Also, the focus of most of the studies was primarily diagnostic and not targeted therapy, championed by precision medicine. While these studies focused on some aspect of musculoskeletal infection, no study has explored the possibility of precision medicine in FRI.

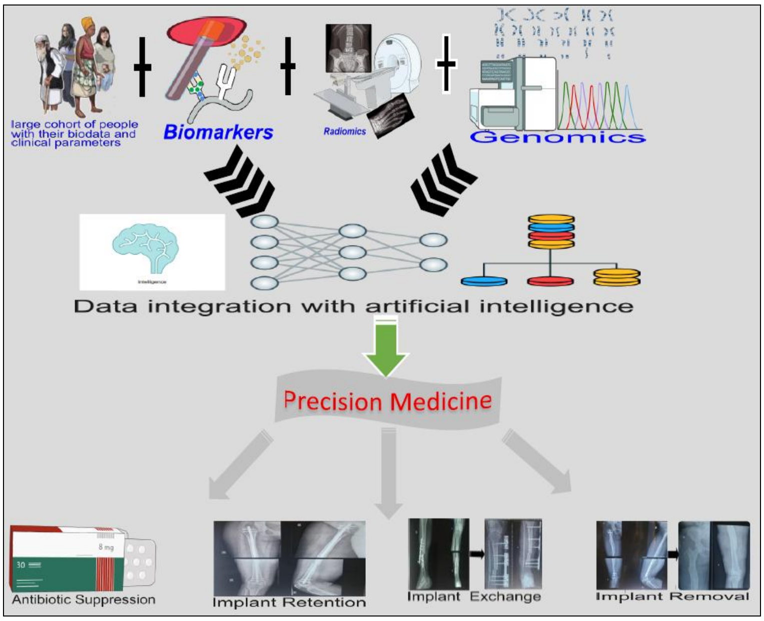

Fig 1: showing the framework for achieving precision medicine in fracture-related infection

Framework for Achieving Precision Medicine in Fri

The architectural framework for achieving precision medicine in FRI is shown in fig. 1. The framework involves integration of clinical data from a large cohort of patients with biological and radiological investigations, and using machine learning for data processing.

Clinical Parameters

From the literature, there are several factors associated with FRI. These factors are generally grouped into patients, fracture, wound and environmental characteristics. These factors are age, gender, smoking status, comorbidities, body mass index (BMI), injury mode, time of injury, presence of polytrauma, fibula fracture status, presence of bone loss, other major injury, compartment syndrome, Gustilo-Anderson classification, wound contamination, irrigation solution, wound location, time to soft tissue cover, type of soft tissue cover, time to definitive fixation, bone grafting at initial surgery, blood transfusion, type of anaesthesia, American Society of Anaesthesiology (ASA) classification, and type of fixation (25-27) A review of the available systematic reviews and meta-analysis on risk factors for FRI consistently showed that male gender, smoking status, diabetes, open fractures, Gustilo-Anderson classification, ASA classification, fixation types, and operation time were significantly associated with FRI [28] Age, BMI, compartment syndrome, wound contamination, wound cover, and polytrauma were not consistent risk factors. All these factors were identified through traditional regression models using a P-value-based method. The result of this method, however, is affected by the risk of type 1 error and important missing variables that are consequence of small sample size. Most modern machine learning models have feature selection methods that select the most important variables necessary for training of machine learning models Hence, all the identified clinical variables are potential candidate predictors that can be combined with other data sources to develop a precision medicine model for FRI.

Gemonics And Polygenic Risk Score

Genomics is a key component of precision medicine. It usually involves human genome sequencing, and identification of genetic variants in the human genome that is associated with specific traits, phenotypes, or diseases [29, 30] This is usually achieved through a Genome-Wide Association Studies (GWAS) where patients with a particular trait or disease and those without are recruited, and through genotyping, Single Nucleotide Polymorphism (SNP), which are prominent in those with the disease but not in those without, are identified. A polygenic risk score (PRS) is then calculated to assess the relative risk of individuals developing the particular trait or disease [31]. Genomics has found wide applications in neonatal screening, precision oncology, pharmacogenomics, and other rare diseases [32]. Genomics and precision medicine have also been applied to specific pathologies in orthopaedics like osteoarthritis, osteoporosis, rheumatoid arthritis, and peri-prosthetic joint infection [33, 34] There are, however, no current GWAS on FRI to identify possible SNP. Therefore, the integration of genomics into the present framework may not be possible. In the future, however, when GWAS becomes feasible and available, the identified SNP can be integrated with other data to update the framework.

Biomarkers Selection

There are several biomarkers that have been identified as possible predictors of FRI, each with varying diagnostic characteristics. The challenge is deciding whether all the biomarkers already linked with FRI should be used in the framework or few selected ones. While earlier reports [35, 36] showed that the diagnostic accuracy of the conventional inflammatory serologic markers (CRP, ESR, WBC) could reach 100% in predicting FRI, more recent studies have cast shadows on their clinical utilities and applications [37]. These biomarkers are however cheap and easily accessible.

There are newer biomarkers with promising results that are being investigated as predictors of FRI. prominent among these newer biomarkers are procalcitonin and interleukin-6 (IL-6). Others are serum calcium, platelet count, platelet derived growth factor AB/BB (PDGF-AB/BB), vascular endothelial growth factor-A (VEGF-A), albumin, and infection-related markers (i.e., neutrophil CD64 (nCD64) and CD66b) [38-41]. These newer tests, however, require sophisticated equipment for analysis, and they are expensive. Hence, their clinical applications may be limited to centers equipped with such facilities. Byrnes and colleague [42]. proposed a framework for selecting the most appropriate biomarker for diagnosing a disease-state, and this borders on ease of sample collection, sensitivity, specificity, sample type, test stability over time, ambient storage temperature, consideration for low resource settings, and most importantly, cost. Using the aforementioned criteria, CRP, WBC, and ESR still fit the biomarkers most appropriate for predicting FRI.

Radiological Investigations

There are several imaging modalities available for the diagnosis of FRI, each offering unique advantages and disadvantages. Each imaging technique has important features that can be extracted and combined with other clinical parameters for a precision medicine in FRI. However, not all the imaging modalities will be suitable for the specifics of precision medicine due to peculiar limitations [43]. While most of the nuclear medicine studies like the Gallium scan, the three-phase bone scintigraphy scan, the White blood cell scintigraphy scan, and ^{18} FDG-PET scans, boast of higher sensitivities, low to intermediate specificities, they are mostly expensive, time consuming, difficult to interpret and some even have low diagnostic value [43]. Ubiquicidin scan, unlike others, have high diagnostic value, but like others, it is expensive and time consuming [44]. MRI can detect inflammatory process early, but its use is limited in post-operative/posttraumatic conditions. It should be avoided in conditions where metallic implant is in-situ, and it may also not be available in all centers [43].

Plain radiographs are cheap, fast, and readily available, though they have low sensitivity and specificity. These limitations notwithstanding, they are very good for assessing osseous changes during follow-up [43]. Radiologic signs of FRI such as radiolucent lines, periosteal reaction, delayed healing, non-union, and implant failure are easily assessed on plain radiographs [45]. Also, the severity of the injury using the AO/OTA classification system can easily be assessed. Hence, the unique characteristics of plain radiographs (cheap and availability), compared to other imaging modalities, makes it a radiologic investigation that can be utilized in the framework for precision medicine. The preoperative severity score, coupled with subsequent post-operative radiologic features suggestive of FRI, can be combined with other clinical parameters to achieve a precision medicine for FRI.

The Framework Architecture

Using machine learning to achieve precision medicine in FRI involves sequence of steps (fig. 2) which are study design, data collection, data cleaning and preparation, data pre-processing and feature engineering, algorithm development, internal validation, and external validation. Each of these steps are discussed below.

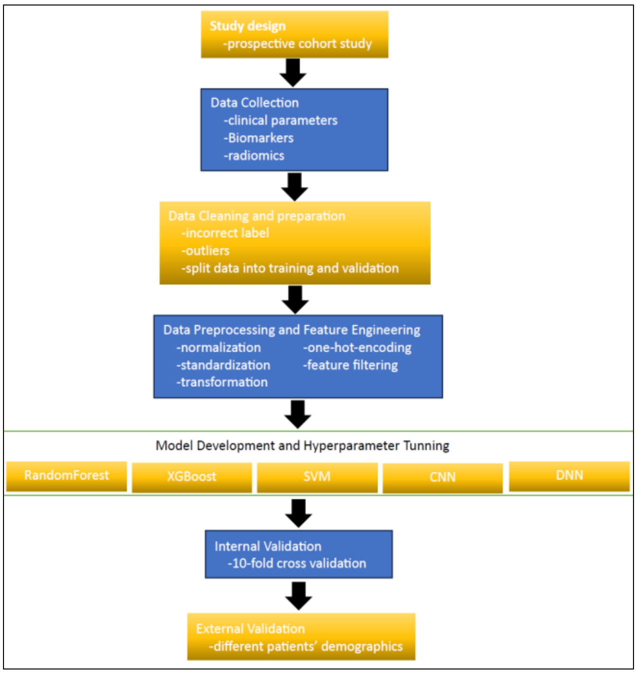

Fig 2: showing the framework architecture. SVM - Support Vector Machine, CNN - Convolution Neural Network, DNN - Deep Neural Network

Study Design

The study design can be a prospective or a retrospective design, though each design has its pros and cons. The prospective design enables pre-specification of what data to collect, collection of all required datapoints, and regular follow-up of the patients in the cohort. This design, however, may require a longer time to complete, leads to loss of patients during follow-ups, and may introduce bias in the surgeon's decision-making process. A retrospective design, on the other hand, will take a shorter time to complete the study, and there will be minimal influence on the decision-making process of the surgeon. But the collection of all the required datapoints may not be possible, since this would not have been pre-specified. Also, a protocol may not have been defined a priori for a retrospective design which may have introduced a lot of bias in patients' recruitment and management. Considering the importance of study protocol and minimizing bias as much as possible, the data can be prospectively collected and retrospectively analysed.

Data Collection

According to the FRI consensus group, there are four options for FRI management which are antibiotic suppression alone or in combination with implant retention, implant exchange or implant removal, after implementation of the requisite management principles. These four options of management will constitute the four groups that the patients will be divided into. It is possible that some patients may require a combination of these four options of management before complete eradication of the FRI is achieved. It is however the first option of care, after critical evaluation of each patient's scenario, that will determine the group the patient will fall into. Important predictor variables and outcome variable will be collected from each patient. The predictor variables will include consistent risk factors previously identified to be significantly associated with FRI. these are baseline demographics (male gender, smoking status, diabetes), clinical parameters (open fractures, Gustilo-Anderson classification, ASA classification, fixation types, and operation time), biomarkers (CRP, WBC, and ESR), and important radiologic features (as radiolucent lines, periosteal reaction, delayed healing, non-union, OA/OTA classification, and evident implant failure). In a sensitivity analysis, the inconsistent risk factors (Age, BMI, compartment syndrome, wound contamination, wound cover, and polytrauma) may also be added to determine if these factors have additional contributions to predicting individualized treatment of FRI. some of these variables will be collected once, while others will be collected at baseline, and during follow-ups. All these data are prospectively collected and entered into a spreadsheet.

Data Cleaning and Preparation

At the end of the study and before analysis of the data is commenced, the collected data is thoroughly checked for accuracy and cleaned as appropriate. The data is checked for incorrect data entry, data with high number of missing values (e.g. $\geq$ 50%), and incorrect categorization or labelling. After the data has been accurately checked for errors and data integrity ensured, the data is split into two using the 80:20 percent rule: 80% of the data is used for development set, while the remaining 20% is used for validation set.

Data Pre-Processing and Feature Engineering

Data pre-processing and feature engineering involves addition, deletion and data transformation, and these processes are very important for improving model performance. These processes usually involve normalization, standardization, transformation, missing value imputation, one-hot encoding, feature filtering, and dimensionality reduction [46]. There are several packages in both python and R software that can be used to achieve these processes. Examples include, SciKit-learn, Feature-engine, Boruta-py, recipes and Boruta. These processes ensure that the data are well prepared and ready for model development and algorithm testing.

Machine Learning Models Development and Hyperparameter Tunning

Developing a machine learning model for precision medicine in FRI requires a multi-class classification, considering the surgical options recommended by the FRI consensus group. While there are several machine learning models, RandomForest, XGBoost, Support Vector Machine (SVM), Convolution Neural Network (CNN), and Deep Neural Network (DNN) are considered top choices for multiclass classification problem [47]. Each of these models can be developed using either Python or R software, the two most commonly used software for machine learning applications. It is usual to use all of these models on the development set, and compare the performances of all the models using evaluation metrics. Each of the models has hyperparameters that can be maximized for optimal model performance, and these hyperparameters, sometimes specific to each model, has to be set before training commences. This hyperparameter tunning can be implemented using either grid search or random search [48].

Internal Validation

One major problem with model development in machine learning, like another model development, is overfitting. This usually occur when a model performs very well on a development (training) set, but performs poorly on a new set different from the development set [49]. To overcome this challenge, the model is internally validated. The two most commonly used approach for internal validation are k-fold validation and bootstrapping. Internal validation helps to check the accuracy and reproducibility of the model [50].

External Validation

External validation assesses how the learned model is generalized to new dataset that has different patients' demographics, but is "plausibly related" to the development set. It measures whether the model can be "transported" to new patients in a different region and clinical setting. This is important to avoid severe sequalae that can occur with erroneous judgement or biased prediction that can occur with the model on new patients. Hence, the new developed model is tested on new patients or dataset that is completely different from patients used for model training, though plausibly related to it. If model performance and evaluation show comparable calibration and discrimination at external validation, then the model is considered safe and generalizable, and it can be deployed for clinical use [50].

Possible Challenges

While this framework proposes a pathway to precision medicine in FRI, it is important to highlight possible challenges to effective implementation.

First, a precision model for FRI is one that is generalizable to all races in all regions. A suitable study design for such generalization will be a multicenter, multi-country study. To achieve this requires strong collaboration among major institutions that cut across developed and developing countries. This is necessary for appropriate data sharing, data collection, and data repository. Currently, such strong collaboration does not exist. While the proposed framework is simplified to ensure that the study protocol can be implemented in the least equipped center, it is only a strong relationship among participating centers that will ensure collection of data that is generalizable.

Secondly, the project may take some time to complete. This is because FRI is rare, and it takes time to develop. Even after its occurrence, it requires time for follow-up. Because of the rarity of FRI and the large sample size usually required by machine learning models for better model performance, a large number of FRIs will be desirable, and it may take time to reach the desired number.

Lastly, a project of this magnitude, like similar projects, will require a great deal of funding. Considering the patient's cohort, the number of participating centers, the time demand, the collaborative effort, and the logistics, it will require huge financial support.

Conclusion

FRI has devastating effect on the patient and the managing team. Ability to precisely predict which patient is at risk of FRI, and also determine the best option of treatment for such patient will greatly improve the outcome. The initiative of precision medicine is well recognized in cancer treatment and another ailment, but this concept has not been fully explored in FRI management. A framework to guide the steps for exploring precision medicine in FRI is therefore necessary at this point. Artificial intelligence is invaluable to the goals of precision medicine. The ability of machine learning to learn intricate patterns from multiple high-dimensional data sources, and find the interrelationship between them, makes them invaluable tools in achieving the goals of precision medicine. There are challenges that will be encountered while attempting to implement this framework, but these challenges are not insurmountable.

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