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Review

Machine learning, infection, microbial toxins profile and health monitoring pre/post general surgeries during COVID-19 pandemic

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Abstract
Although almost 2 years have passed since the beginning of the coronavirus disease 2019 (COVID-19) pandemic in the world, there is still a threat to the health of people at risk and patients. Specialists in various sciences conduct various research in order to eliminate or reduce the problems caused by this disease. Surgery is one of the sciences that plays a critical role in this regard. Both physicians and patients should pay attention to the potent steps of different infections' key-points during pre/post-general surgeries in the case of preventing or accelerating the healing process of nosocomial acquired COVID-19. The relationship between COVID-19 and general surgical events is one of the factors that could directly or indirectly play a key role in the body's resilience to COVID-19. In this article, we introduce a link between pre/post-general surgery steps, human microbial toxin profiles, and the incidence of acquired COVID-19 in patients. In linking the components of this network, artificial intelligence (AI), machine learning (ML) and data mining (DM) can be important strategies to assist health providers in choosing the best decision based on a patient's history.

Keywords: COVID-19, General Surgeries, Microbial toxins, Machine learning

1. Introduction

In the two years since the coronavirus disease 2019 (COVID-19) pandemic, elective and emergency surgeries have been influenced by various health protocols [1]. There is frequent asking question that says "Is It Safe to Have Surgery after COVID-19 Infection?" and studies suggest that elective surgeries should be delayed, when possible. It is now obvious that the lasting effects of COVID-19 can affect human health in different ways via different routes and including body maintenance and reactions to surgery. In this case, the changes could be significant. Studies have shown a substantial increment in the risk of postoperative death and pulmonary complications

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(Six weeks after symptomatic and asymptomatic COVID-19 infection). In fact, if we look more closely at the issue of infection in surgeries, we will see that this is not a new issue at all. In fact, even before the onset of the COVID-19 pandemic, surgical wound infection was an important issue for medical systems. The infectious agents can infect the patient before, after or during surgery. In hospitalized patients, wound infection is the second most prevalent cause of nosocomial infections [2, 3]. The risk of these infections ranges from 2 to 20%, depending on the facility, the patient, the condition, and the kind of operation [2]. Surgical wound infection can increase the time of patients hospitalization. Approximatly, 60-80% of infections are related to the wound site. Infections are often diagnosed using one of the following criteria: 1) Wound discharge that is purulent, 2) the presence of microorganisms from the wound discharge and 3) removal of purulent discharge from the wound site [4]. According to a global standard, wounds are classified into four groups, depending on the extent of the infection at the time of surgery: 1) a clean wound: non-infectious and non-inflammatory, 2) clean but infected wound, 3) infected wound: which is fresh wounds, is open or due to accident trauma and 4) Dirty infectious wounds: old wounds caused by trauma with dead tissue or perforated viscera [5]. Wound classification can also be a predictor of wound infection and is therefore very important [6]. Past studies have shown that in 30% of surgeries, glove rupture occurs, which in turn leads to wound infection originating from the operating room [6]. Age, surgery in more than one anatomical location, increased duration of surgery, longer surgical wound length, surgery due to malignancy or rupture of viscera, history of hypertension, history of diabetes mellitus, using narcotic substances (drug), consumption of alcohol, recent steroid use, recent history of chemotherapy, low serum hemoglobin and albumin are among the predisposing factors for wound infection in patients have been mentioned [7].

In this study, we look at several microbial agents and their byproducts that might cause infection before, after, or during surgery. We believe that machine learning will be a beneficial methodology for categorizing, diagnosing, or forecasting surgical wound infection as a novel strategy.

2. Surgery site infection, microorganisms and their secondary metabolites

Various microorganisms are known to cause surgical wound infections. the most prevalent isolated organisms are a group of bacteria like *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp., *Escherichia coli*, *Acinetobacter* spp., *Klebsiella pneumoniae*, *Proteus* spp., *Morganella* spp., *Citrobacter* spp., some anaerobic isolates and *Pseudomonas aeruginosa* (in the case of burned wound infection) [2, 8]. Many of these bacteria are resistant to antibiotics, which is an important problem in treating wound infections [9]. Many of these bacteria complicate the healing process by forming protective structures such as biofilms [10]. On the other hand, the production of bacterial secondary metabolites such as toxins, along with antibiotic resistance, is another fatal blow that bacteria inflict on humans during wound infection [11].

Another very important point to consider in the management of wound infection is bacterial toxins. Unfortunately, not many studies have been done in this regard, and the mechanism of toxicity of the bacteria that cause wound infection has many unknowns; this is a very important issue. It is critical to note that killing the bacteria does not necessarily mean removing its toxin from the body. For example many Gram-negative bacteria have toxins such as endotoxin (lipopolysaccharide = LPS) that even if killed with the correct sensitive selected antibiotic, their toxin is still released and will have systemic effects on patients [12]. Many common wound-infecting bacteria's toxin, such as *S. aureus*, is also a super-antigen and may cause deadly shock effects in a short period of time and at extremely low concentrations. This means that even the slightest level of wound infection should not be taken lightly [13]. Some bacteria, such as *P. aeruginosa* and *E. coli*, also have great diversity in some secondary and toxic metabolites, such as pigments and cytotoxic toxins. Some of these toxins are even resistant to the heat that normally kills bacteria [14]. Therefore, it is recommended to pay attention to the symptoms of microbial toxicity in the patient along with the symptoms of general bacterial infection in order to achieve effective treatment in surgical wound infection.

For better clarification, we are briefly reviewing the pathogenesis steps of bacteria: 1) Binding of bacteria to cellular receptors (commonly referred to as colonization), 2) Proliferation (at this stage, bacteria have different defense and invasive strategies such as biofilm production or secrete toxins), 3) Dissemination (proliferated bacteria or produced microbial toxins will distribute systemically in the body) and 4) Transmission (at this stage the bacterium is able to transfer to a new host) [15].

At different stages of wound infection, bacteria and their toxins can cause different clinical effects in patients [16].The type of clinical effects observed in patients can depend on several factors and depend on patient or pre/post operation different risk factors. Some of the most important items in this case include: 1) the type of bacteria and toxin produced, 2) the active (vegetative) or inactive form of the bacterium (spore) that was initially colonized in the wound, 3) the mechanism of action of the toxin released from bacteria at the site of infection (neurotoxic, cytotoxic, enterotoxic, etc.), 4) the strength and readiness of the patient's immune system, 5) careful selection of effective and sensitive antibiotics before and after surgery, 6) regular and accurate monitoring of the patient after surgery, 7) poor nutritional state and habits of the patient's daily life like being current smoker or level of personal hygiene by the patient , 8) extremes of age and occupation of the patient, 8) Presence of underlying diseases or use of immunosuppressive drugs, 9) proper nursing care of the wound, 10) observance of aseptic conditions before, during or after surgery or at the time of nursing care of the wound after surgery or while surgery draining [17]. Depending on each of the above, different clinical symptoms can be seen in patients.

Clinical signs of a surgical site infection usually present 5-7 days after surgery, but they might appear up to 3 weeks later (especially in the case of the prosthesis insertion). The most prevalent are: spreading erythema, localized discomfort, pus or discharge from the incision. Wound dehiscence and persistent pyrexia, as previously reported [18]. The majority of surgery site infections (SSIs) are superficial, however some are deeper and can result in significant wound collapse. Fortunately, in clinical practice, the requirement for debridement and open wound treatment is uncommon [19]. Aseptic wound swabs should be collected for culture at the wound site for any SSI infection, especially if a purulent discharge is evident. It is critical to prevent wound edge culturing wherever feasible in order to reduce skin flora contamination. It is also critical to do blood tests for infection indicators (FBC, CRP) [20]. It is advised to be used if there is any sign of systemic involvement or sepsis. Inflammatory cytokines (IL-6, IL-1, TNF-a) and platelet indicators such as platelet count, mean platelet volume (MPV), and mean distribution weight (MDW) might help predict the likelihood of endotoxemia and septic shock [21].

3. Applied Machine learning (ML)

Choosing the best diagnostic method is always one of the major concerns of medical systems [22]. A good way to predict the severity or occurrence of an infection is to categorize clinical and laboratory data and information using computer knowledge. Artificial intelligence (AI), in this situation, machine learning (ML) and data mining (DM) are three multipotentially relevant methodologies.

These sciences can be summarized as follows: AI as a subset of ML, is an area of computer science that employs automated computing processes, reasoning, and inferencee by computers. Main application of ML is to converts data into information and makes logical decisions through this conversion. The most important algorithms in these conversions are as follows: classification, clustering, feature selection and prediction. On the other hand, DM is a way to extract information from a big data. It is not a technical discipline but uses different algorithms related to natural language processing (NLP), ML and AI. DM have the ability to search and compare different data of obtained from different programs, texts bodies, summaries and create a unique question-answer systems for categorizing and classifying data to make reasonable conclusion [23]. We can utilized these computer sciences to write specific algorithms and help computers to behave intelligently to perform various tasks.

As mentioned previously, ML has the potential to generalize data from a lot of information and can utilize calculations to recognize connections between data. DM, AI, and ML are three sciences that, can be of great help for physicians in the manner of diagnosis and prediction process if they are given the right data and asked the right request based on a logical algorithm [24].

By the use of state of the art lab technologies, modern medicine produces mass data obtained from infection cases. ML and DM has the ability to analyze raw/multidimensional data of wound abnormalities, microbial toxicity, tissues charges and patient lab information that is available at databases of hospitals or clinical labs. After targeted classification, these information and data could present regular patterns involved in SSI development. Yielded computing data is useful to introduce and determine correlations between different characteristics such as patients' personal data, disease symptoms or even disease predictions. One of the most important aspects of ML in the case of data analysis is helping physicians to diagnose infection symptoms more accurately and choose the appropriate treatment for patients with significant changes in their surgery site morphology and histology (Figure 1) [21, 25].

Today, the use of technology and science of ML in the prevention, early diagnosis and treatment of many infectious disease like sepsis and many neurological diseases such as Alzheimer's, dementia or Parkinson's is underway [26]. For example Sepsis, consider as the most important disease at the first 28 days of life and is one of the main causes of neonatal death in the intensive care units [18]. This neonatal infection is known as a nosocomial infection. Because most of these infections are resistant to antibiotics, they can be a major cause of clinical non-response to treatment and the rapid spread of sepsis and septic shock, multiple failures, and increased mortality in hospitals. Acinetobacter is an important opportunistic bacterium that is widely distributed in hospitals and is a major cause of nosocomial infections. Because it quickly becomes resistant to major groups of antibiotics, such as penicillin, it is difficult to treat. Given the importance of rapid diagnosis of neonatal sepsis, the researchers conducted a study of sepsis with an infectious agent that examined Acinetobacter in neonates admitted to the intensive care unit using ML modeling. To conduct this study, they first searched for databases, clinical findings, laboratory findings, arterial blood gas, vital signs, comorbidities, and sepsis invasive procedures. After extracting this data, the list containing 75 features of more than 4,000 infants was extracted and analyzed using machine learning [27].

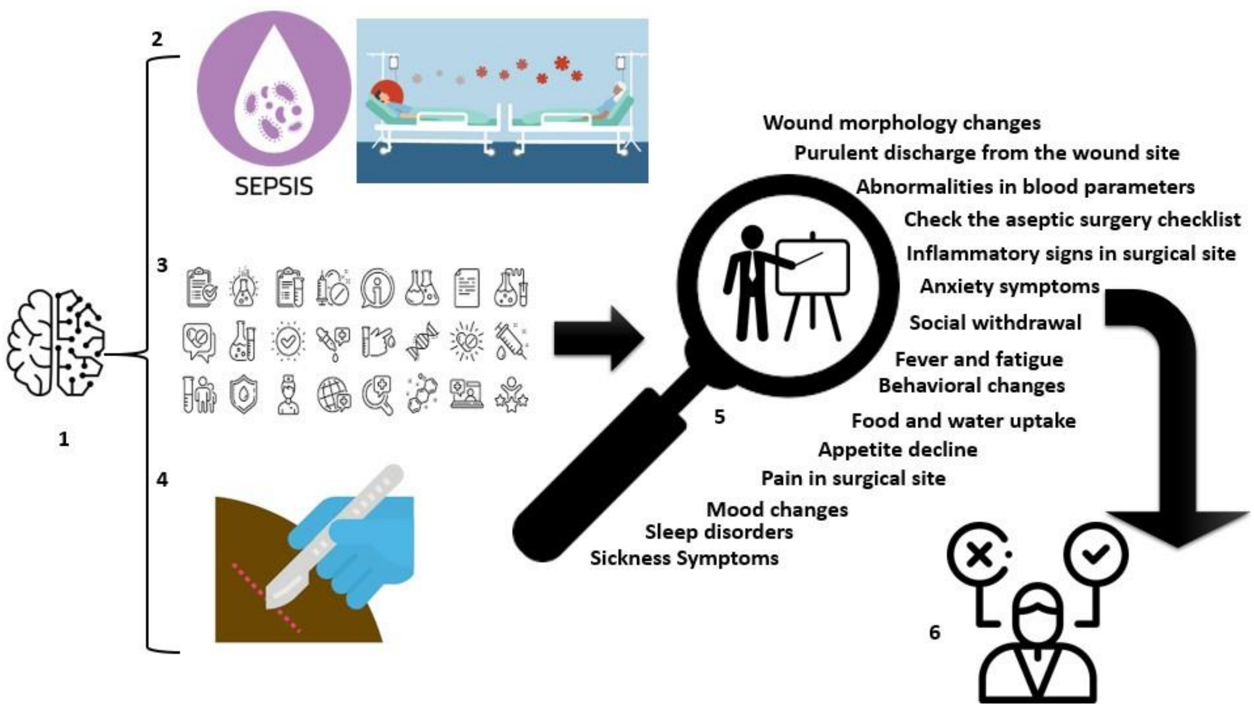

Figure 1. Application of ML in COVID-19 SSI prediction. 1) ML models will develop for analyzing classified and categorized different libraries of patients disease information include: 2) COVID-19 symptoms, sepsis and bacterial toxemia markers, hospital-acquired infections criteria, 3, 4) SSI and other postoperative infections indexes, Microbiological test results, molecular biologic test results, blood and other clinical samples biochemistry results, types of antimicrobial prescription and microbial resistance, monitoring and tracking of site-specific infections, 5) Finding explanations based on analysis and going through predictions based on analysis results and finally, 6) Held best decision.

In other studies, other factors such as gestational age and vital signs, positive blood culture, lactate, systolic blood pressure, gestational age, birth weight, mechanical ventilation, complete feeding and blood transfusion, lethargy and malnutrition and finally sex of the baby applied to predict sepsis in infants [27].

ML is also used in SSI evaluation and prediction. For example a simple algorithm for monitoring women after cesarean section has been written. Machine learning uses the score obtained from each of the questions asked of the patient and can be very helpful in predicting infection at the surgical site. Such an application and achievement of machine learning in rural areas, which are far from many medical centers, and the world today, which is involved with the COVID-19 pandemic, is significant and very important [6, 18]. In another study, ML was used to assess the severity of infection progression in superficial SSI, Organ/Space SSI, and total SSI. In this investigation, the following factors were significant for assessing the identification of superficial, organ, and total SSI: SSI-related imaging, SSI-related treatment, SSI-related International Classification of Diseases (ICD), *Corynebacterium*, *Enterococcus*, *Staphylococcus*, *Streptococcus*, superficial SSI antibiotic, organ SSI antibiotic, fluid, abscess, wound minimal partial thromboplastin time, systolic blood pressure, and temperature [21]. Text mining (TM) and ML were employed to predict SSI in another study published by Silva et al [23]. In their study, descriptive datasets included: the number of patients, the mean (and standard deviation) of patients' ages, the average number of surgeries per patient, female patients, the mean (and standard deviation) of female patients' ages, male patients, the mean (and standard deviation) of male patients' ages, and the average number of surgeries per patient. The number of surgical procedures, the number of elective procedures, the number of urgent procedures, the number of emergency procedures, and the average (and standard deviation) of the surgical team.

In this investigation, the following algorithms performed well in predicting SSI: Logistic Regression (LR), Multinomial Naive Bayes (MNB), Nearest Centroid (NC), Random Forest (RF), Stochastic Gradient Descent (SGD), Support Vector Classification (SVC), and Linear SVC are all examples of support vector classification algorithms [23]. ML even have used for screening COVID-19 as a quick and efficient tool based on subjects symptoms and exploration of COVID-19 mortality risks [21]. Scientist believe that early mortality prediction using non-invasive ML models are a promising revolutionary method. On the other hand, the application of ML in connection with the diagnosis of SSI is developing every day and these methods could be very useful in telemedicine systems during COVID-19 pandemic.

4. Conclusion

If the infection at the surgical site is associated with a COVID-19 infection, the treatment becomes more complicated. A successful COVID-19-SSI ML project requires the collaboration of physicians, nurses, laboratory personnel, microbiologists, microbial toxicologists, computer engineers, and programmers. Another important factor in the proper implementation of a ML project related to SSI is the existence of complete information, high sample size and the existence of powerful computer servers for data analysis. These are the things that will increase the accuracy of the results obtained. In the sample studies cited in the text, a number of bacterial factors were examined to assess and predict SSI deterioration. It is suggested that future researchers also use factors related to the clinical effects of toxins produced by bacteria to increase the accuracy of their prediction results. Researcher could consider different variables during intraoperative, post-operative or pre-operative phases as critical stages of infectious agent or bacterial toxins entrance to the surgery sites that lead to better variables selection. Ultimately, the progression of telemedicine by developing ML for medical care presents potential, and having a positive impact on SSI care and surgical quality improvement especially in rural area during COVID-19 pandemic.

Authors' contributions

MJ: Collecting and summarizing machine learning articles. KA, SH: Collecting and summarizing infection articles. AB: Collecting and summarizing microbial toxins profile articles. AR: Collecting and summarizing health monitoring articles. MM: Drafting, EndNote library preparation and referencing manuscript body. SM: Collecting and summarizing Both Microbial toxins and Health Monitoring articles. EGH, AR, AM: Edit files based on reviewers comments, suggesting the idea of article, writing first

draft of article, scientific editing and native language editing.

Conflict of interests

The authors reported no potential conflict of interest.

Ethical declarations

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