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Artificial Intelligence approaches in hematopoietic cell transplant: A review of the current status and future directions

Running Title:

Artificial intelligence in BMT

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ABSTRACT:

Currently, the evidence-based literature on healthcare is expanding exponentially. The opportunities provided by the advancement in artificial intelligence (AI) tools i.e. machine learning are appealing in tackling many of the current healthcare challenges. Thus, AI integration is expanding in most fields of healthcare, including the field of hematology. This study aims to review the current applications of AI in the field hematopoietic cell transplant (HCT). Literature search was done involving the following databases: Ovid-Medline including in-Process and Other Non-Indexed Citations and google scholar. The abstracts of the following professional societies: American Society of Haematology (ASH), American Society for Blood and Marrow Transplantation (ASBMT) and European Society for Blood and Marrow Transplantation (EBMT) were also screened. Literature review showed that the integration of AI in the field of HCT has grown remarkably in the last decade and confers promising avenues in diagnosis and prognosis within HCT populations targeting both pre and post-transplant challenges. Studies on AI integration in HCT have many limitations that include poorly tested algorithms, lack of generalizability and limited use of different AI tools. Machine learning techniques in HCT is an intense area of research that needs a lot of development and needs extensive support from hematology and HCT societies / organizations globally since we believe that this would be the future practice paradigm.

INTRODUCTION:

Around sixty years ago, Dartmouth conference had set the bases to “Artificial Intelligence (AI)”. The name was coined to the use of technology in accomplishing tasks that usually need human intelligence. These tasks include, but are not limited to, interpreting language, making decisions and visual perception [1,2]. Soon after the conference, AI field started to develop exponentially. One major example was “Dendral” of Stanford University that started in the early 60s. Dendral used heuristic programming to provide solutions in the field of science [3].

Integration of artificial intelligence in medicine started around a decade after the Dartmouth conference [1]. “MYCIN” was one of the early medical programmes developed from Dendral to detect bacteria causing the infection and to decide on appropriate antimicrobials and their doses. This program had achieved a rate of agreement of 60% when compared to the decisions given by expertise. Despite of the suboptimal rate of agreement, it was able to cover all treatable pathogens and showed to decrease the number of antimicrobials used [4]. This was followed by many other AI tools, such as Internist-I, that were developed to help medical practitioners [1,5].

The use of AI in medicine has led to a debate on how beneficial AI is in improving medical practice. Advocates of such integration list advantages such as, increasing efficiency and helping medical practitioners to practice the real meaning of medicine. On the contrary, opponents of such integration attribute their opposition to different disadvantages that include concerns about accuracy of these systems, risk of having “deskilled” physicians and less future jobs especially for diagnostic medical fields such as radiology and pathology [6,7].

Despite of the possible disadvantages and skepticism, the increasing complexity of medical practice and the opportunities provided by the advancements in AI, make the integration inevitable. Thus, growing numbers of projects have tried to integrate the tools that AI provides into the different fields of medicine including hematology and oncology. Examples of integration are numerous, for instance, *Watson for Oncology* (WFO) is a project created by the International Business Machines (IBM) which can cope with the expanding evidence and to learn from cases [8]. The project’s results are promising, for example 93% level of concordance was achieved by WFO when compared to physician-led tumour board decisions for breast cancer treatment plans. This level was even higher in stages II and III of breast cancer [9]. The use of AI in the fields of haematology and oncology are not limited to treatment decisions and plans, for example different studies have investigated the use of AI in leukemia diagnosis, management and prognosis [10-12].

The field of hematopoietic cell transplant (HCT) is expanding, with more than 60,000 procedures being performed annually worldwide [13]. It is also estimated that by 2020, the world will have half a million HCT survivors [14]. The rapid expansion of the field necessitates the need of augmenting the tools that are provided by AI to increase efficiency and improve patient care. Thus, this review aims to investigate the status of AI integration in the field of HCT and list some future directions and research agenda.

METHODS:

The literature review used Boolean logic with terms including: "Machine learning", "Deep learning", "Neural Networks" and "Artificial intelligence" in combination with terms specific to the field of hematopoietic cell transplant such as: "Bone marrow transplant", "Hematopoietic cell transplant", "Graft-versus-host disease" etc. The search targeted the last 10 years due to the growth of the AI field into hematology, oncology and HCT. The following databases were used: Ovid-Medline including in-Process and Other Non-Indexed Citations and google scholar. The abstracts presented at the annual meetings of the following professional societies: American Society of Haematology (ASH), American Society for Blood and Marrow Transplantation (ASBMT) and European Society for Blood and Marrow Transplantation (EBMT), were screened as well to avoid file drawer bias. Terms that were used to screen the abstracts were: "Artificial intelligence" and "Machine learning".

RESULTS:

The number of abstracts investigating the use of artificial intelligence in the field of hematology has increased over years. Figure 1 shows the number of abstracts presented in the field of AI in three major haematological societies' meetings (ASH, ASBMT and EBMT) from the years 2010 to 2017. It can be noted from the figure, that the number of AI abstracts presented in these meetings have increased 8 times between the years 2010-2017. This increase indicates the increasing focus and advancements on the potential uses of AI in hematology. On the other hand, the number of abstracts presented in the field of HCT increased from none in 2010 to 5 in 2017.

Literature search revealed many studies which investigated the use of AI tools in improving different aspects of HCT. The studies have targeted both pre and post-transplant applications, and are discussed below.

Pre-transplant applications:

Selection of donor-recipient pair for HCT is a major challenge that could affect prognosis of HCT recipients. The presence of a HLA-matched sibling can be found only in 30% of cases of HCT in the United States (US) [15]. Lee et al. found that one loci mismatch in donors can decrease 1-year survival to

43% from 52% in fully matched recipient-donor pair, this risk increases when more loci mismatch present [16]. Different studies investigated the possible use of AI methods and tools to tackle this challenge. Marino et al. [17] identified 19 amino acid substitutions that are related to at least one bad outcome post-HCT using random forest and logistical regressions methods. This includes overall survival, treatment related mortality, incidence of GVHD etc. However, none of these substitutions was able to pass the validation in an independent cohort. This was also the case of a recent study by Buturovic et al. [18] in which different factors that included donors', recipients' and transplantation characteristics were used to create an algorithm using machine learning (ML). This algorithm aimed to increase survival of HCT recipients secondary to acute leukaemia by improving selection of the donors. Despite of the optimistic preliminary results, the algorithm failed the validation study.

More methods have been proposed to develop algorithms that can help in the selection of donor-recipients pair. For instance, two abstracts [19, 20] have proposed the use of different ML tools to aid this process. Sarkar et al. developed an algorithm that used both HLA and killer-cell immunoglobulin-like receptor (KIR) to improve the selection of donors for recipients with acute myelogenous leukaemia (AML). The algorithm was able to increase the accuracy of predictions by 3-4%, when it was compared to the usual analysis [19]. Sivasankaran and colleagues [20] proposed using a black box model in developing a system which uses secondary non-HLA characteristics in selecting donors, though no data on validation or improvement of accuracy was reported up-to-date.

Post-transplant applications:

Despite of all the advances in HCT, Recipients of HCT are at risk of many complications that might increase their mortality and morbidity including GVHD [21,22]. Thus, predicting recipients' risk of developing these complications and their prognosis would aid clinicians to make better decisions that would improve patients' quality of life [QoL] and survival.

One of the major projects in this field is AL-EBMT. In 2015, EBMT developed acute leukemia (AL)-EBMT predictive model to stratify acute leukemia patients according to their prognosis post-allogenic hematopoietic cell transplant [23]. AL-EBMT (accessible using: http://bioinfo.lnx.biu.ac.il/~bondi/web1.html) [24] was externally validated using Italian transplantation network cohort (GITMO). The results showed that AL-EBMT is a valid tool in stratifying risk of AL patients undergoing HCT. It was able to predict day 100 mortality, leukemia free survival (LFS), 2-year overall survival (OS) and non-relapse related mortality with area under the receiver-operator curves ranging from 0.651– 0.698 [25]. However, the tool use cannot be generalized to other non-European populations.

Furthermore, studies have investigated the use of AI tools in predicting outcomes of HCT. Li et al. [26] proposed using AI approach in predicting allogenic HCT outcome in AML and MDS by using pre-transplant minimal residual disease (MRD). MRD detection traditionally takes place using flow cytometry with physicians' interpretations, and this leads to considerable variability in interpretations. An ML approach was tried on a training set and then confirmed using a validation set. The approach was found to differentiate between abnormal (MDS or AML) and normal in 90.8% in training set and 84.4% in validation set. The system was also 100 times faster than experts in getting interpretations of results.

Graft-versus-host-disease (GVHD):

In addition to the use of AI approaches in diagnosis, Gandelman and her team, showed that ML tools offer a chance for classifying cGVHD into new phenotypes that are related to survival [27]. However, this new classification system will need to be validated.

Predicting the development of acute GVHD was investigated by Caocci et al. [28] in 78 thalassemia patients who underwent unrelated allogenic HCT, using artificial neural networks (ANN). ANN was compared to results acquired by logistical regression. The authors found that ANN was significantly more sensitive in predicting acute GVHD in cases who developed it, however no difference was noted in predicting the absence of GVHD. This finding was supported by a recently presented abstract in EMBT [29], which showed the superiority of ML models when compared to classical models such as logistical regression in predicting 100-day treatment related mortalities post allo-HCT. The search yielded very few technical studies that studied and compared the ways and methods to increase the accuracy of AI approaches and tools.

Furthermore, few studies have indicated the limitations we have or methods that will help us to reach optimal use of machine learning. For instance, Shouval and his colleagues [30] had investigated the development of multiple models that is able to predict 100 days non-relapse mortality post HCT. Authors' findings suggested the need of broader data input from patients to be able to increase the predictive ability of AI developed models, this includes biologic and genetic factors. ElHassan et al. [31] investigated the use of different sampling techniques to improve the accuracy of machine learning algorithms. Authors concluded that the use of sampling techniques, including Random Oversampling (ROS), Synthetic-Oversampling Technique (SMOTE) and Remote Under sampling (RUS), improve the accuracy of machine learning algorithm in predicting Day-100 treatment related mortality in allogeneic HCT.

DISCUSSION:

Complexity of healthcare system and the amount of medical literature and evidence have increased tremendously in the last few decades and it is nearly impossible for a practising physician to keep up with all published literature even in a narrow field of practice. This is accompanied with the need of more documentation, especially with the emergence of electronic medical records (EMR) and electronic health records (EHR). These electronic records may have influenced the effectiveness of medical practitioners and can make it difficult for physicians to practice the real meaning of medicine [32, 33]. On the other hand, these tools have made it easier to reach patients' data especially in the case of EHR. In the era of "big data", EHR acts as a source of data that can be used to improve research and healthcare [34, 35]. Moreover, data soon might be regional or even international with the help of registries [36]. Thus, EHR and registries will provide AI systems with sets needed to train and validate the systems. AI systems will also likely revolutionize EHRs, to be more automated thus giving medical practitioners more time to spend with their patients [6, 14].

AI approaches via different tools might be an opportunity to use this "big data" to extrapolate and create beneficial algorithms that can be applied for other patients. Despite many advantages that can be provided by integrating AI in medicine, many disadvantages may also occur. These include endangering some types of medical jobs, possible technical errors and deskilling [6, 37]. Many of these disadvantages might be exaggerated as AI approaches are not alternate but an extension of our currently used statistical tools [38]. These new approaches and tools will play a major role in the future of medicine.

AI integration has shown to be reliable, accurate and promising in various instances. For instance, Weng et al. [39] used different machine-learning approaches to create algorithms that can predict risk of developing cardiac events within 10 years. AI approaches was found to be superior in predicting the risk of developing cardiac events to the established American College of Cardiology (ACC) algorithm. Watson for oncology is another example that holds a lot of potential in improving the care delivered to cancer patients [9]. Improvement in diagnosis and efficiency is also expected in diagnostic fields such as radiology [40]. The implementation of AI seems to be inevitable and more applications will soon be in practice.

Moreover, future research is expected to develop more tools that have more ability in detecting patterns in unstructured and unsupervised data. The concurrent development of tools of data collection, that is more instant and real-time is important to increase the amount of big data. This is evident by the parallel advancements in the field of Internet of things (IOT). IOT will be able to advance our methods in collecting data via connecting the various tools we use in our clinical practice (e.g. wearables, thermometers, stethoscope, etc.) directly to our EHRs and databases [41]. This will be an opportunity for us to use more real time data that will help us to develop more accurate databases that can be later invested by the tools of AI.

In this review however, we demonstrate that the integration of AI in the field of HCT is still an area that needs a lot of development. Published literature did not tackle many important aspects of HCT including the field of survivorship, risk of infections, pharmacogenomics etc. For instance, with the increasing number of HCTs done and improved management, it is expected that there will be half a million HCT long term survivors by 2020 [14, 34], thus AI offers a great opportunity to help providing these patients optimal longitudinal care.

We have summarized many promising pre and post-transplant studies of ML in HCT, however, these studies have many limitations. Most of these studies are still in a preliminary phase; training set done on a small sample size limits power; some of these studies have not confirmed findings with a validation set. Other limitations include the need of technical studies that investigate the efficiency and accuracy of different AI methods and approaches. One of the concerns of using AI in the field of HCT and other medical fields is the generalizability of the systems. A system such as AL-EBMT [23] needs to be validated on other populations to be eligible for use. However, the horizon includes many opportunities especially with the increase in the number of registries and data (e.g. CIBMTR, EBMT). Moreover, AI integration should be supported by the HCT and hematology societies globally, to ensure that AI applications are well validated and can be used. Given the presence of "big data" in the international HCT registries, the HCT community can utilize ML technologies to their benefit to improve both patient outcomes and systems efficiency.

AI integration in HCT is expanding and its role in day to day activities of clinical practice is inevitable. It is time for our research and clinical community to step forward and incorporate ML usage with the existing models. Though this would be cutting edge, AI's integration should be cautious and must target improvements in patients' care rather than focusing on technologic improvements. It should be incorporated in practice, but should not take us away from the *sine qua non* of medicine as an oral science, and our role as healers!

CONCLUSION & FUTURE DIRECTIONS:

- Implementation of AI in HCT is still suboptimal. Future studies should try to involve more data for both training and validation sets. This necessitates more funding and support from different HCT and hematology societies globally as well as from government agencies. This support will allow AI tools to be of a better quality and be generalizable.

- Integration of AI in medicine is inevitable. However, this integration should be cautious and well validated to improve patients' care. Some concerns of AI use are valid and should be considered when using AI tools. AI aim should be to improve medical practice and healthcare.

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FIGURE Legend

Figure 1: Number of AI abstracts presented in ASH, ASBMT and EBMT meetings from year 2010-2017. The number of AI abstracts presented in these meetings had increased 8 times between the years 2010-2017. Whereas, the number of abstracts presented in the field of hematopoietic cell transplant increased from none in 2010 to 5 in 2017.