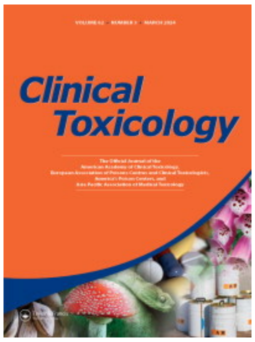

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COMMENTARY

Predicting the outcome in poisoned patients: look at the past!

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ABSTRACT

Introduction: When predicting future events, we often rely on analyzing past occurrences and projecting them forward. This methodology is crucial in various fields, including toxicology, in which predicting outcomes in poisoned patients plays a vital role in guiding treatment decisions and improving patient care.

Importance of predicting outcomes in poisoned patients: In cases of poisoning, understanding a patient's medical history, current physiological status, and the toxicokinetics of the ingested substance is essential for predicting potential outcomes and determining appropriate interventions.

What to predict?: Predicting whether an intoxicated patient needs (further) treatment or even admission to the hospital is one of the most difficult decisions a clinician needs to make. The prediction of the course of an intoxication often lacks crucial information, leaving physicians with a sense of uncertainty in treating and advising patients. A significant source of this uncertainty stems from patients' limited awareness of the specific chemical(s) causing their symptoms, making a targeted approach challenging. Adding to the complexity, both patients and physicians frequently lack knowledge of the exposure dose, onset time, and potential interactions, further complicating the prediction of symptom progression. Patients are commonly placed in observation wards until the pharmacodynamic effects have diminished, leading to extended observation periods and unnecessary healthcare utilization and costs. Therefore, a key objective of a predictive model is to determine the necessity for intensive care unit admission.

Predicting the requirement for admission to an intensive care unit: Factors such as age, Glasgow Coma Scale, and specific comorbidities like dysrhythmias and chronic respiratory insufficiency significantly influence the likelihood of intensive care unit admission. By examining a patient's trajectory based on past medical history and organ function deterioration, clinicians can better anticipate the need for critical care support.

Enhancing prediction models for improved patient care: To enhance prediction models, leveraging modern methodologies like machine learning on large datasets (big data) are crucial. These advanced techniques can uncover previously unknown patient groups with similar outcomes or treatment responses, leading to more personalized and effective interventions. Regular updates to clustering, discrimination, and calibration processes ensure that predictive models remain accurate and relevant as new data emerges.

Conclusions: The field of clinical toxicology stands to benefit greatly from the creation and integration of large datasets to advance toxicological prognostication. By embracing innovative approaches and incorporating diverse data sources, clinicians can enhance their ability to predict outcomes in poisoned patients and improve overall patient management strategies.

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Intoxication; outcome; prediction; modelling; predictive value

Introduction

In our daily lives, we often engage in predicting future events, whether it is forecasting weather patterns [1], predicting stock market performance, or assessing the odds of winning a hand of poker [2]. This predictive process involves analyzing past occurrences to obtain insights that can inform our expectations. For instance, if recent weather conditions have been favourable, it is quite reasonable to expect similar conditions in the near future. However, as we extend our projections further into the future, the level of certainty diminishes.

In medicine, a patient's prognosis hinges on evaluating their health trajectory, encompassing factors such as medical history, co-morbidities, medication regimens, and assessments of frailty. A patient's clinical trajectory is crucial in determining their future health outcomes. For instance, if a patient's health has been deteriorating consistently, it is likely that they will eventually require organ support [3]. Neglecting to consider a patient's history and trajectory can lead to unexpected challenges in providing critical toxicological care, highlighting the importance of a comprehensive assessment.

Whether in daily life or medical practice, the significance of analyzing past events to predict future outcomes cannot be overstated. By understanding the trajectory of events and

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incorporating relevant data points, we can make more informed predictions and decisions.

The importance of predicting outcomes in poisoned patients

Predicting the outcome of poisoned patients serves several critical purposes within the realm of clinical toxicology.

Guiding intervention decisions

Predicting the course of a disease in poisoned patients helps determine the necessity of intervention. This predictive ability is essential as it aids in distinguishing cases that require immediate treatment from those that may warrant further observation. For instance, established guidelines like the Rumack-Matthew nomogram provide thresholds for interventions such as acetylcysteine treatment based on the timed paracetamol concentration [4].

Efficient resource allocation

Anticipating patient outcomes enables the efficient allocation of limited hospital resources, such as intensive care unit (ICU) beds and costly medications, to those in critical need. By accurately predicting whether ICU admission is necessary, healthcare providers can optimize resource utilization, ensuring that resources are available for patients who require intensive care. This strategic allocation was particularly crucial during the COVID-19 pandemic when resource scarcity was an important concern [5]. However, in everyday practice outside the pandemic, difficult decisions must also be made based on resource availability or cost-benefit ratios.

Recognizing futility in treatment

Predicting a patient's trajectory is vital in identifying situations in which further treatment may be futile and recovery is unlikely despite interventions. For instance, exceeding established thresholds, such as that in the paraquat nomogram by Proudfoot et al. [6], can indicate a poor prognosis when survival is improbable, leading to a shift in focus towards palliative care.

Facilitating quality improvement through benchmarking

Outcome predictions, especially related to mortality, facilitate comparisons of treatment efficacy across healthcare institutions. By utilizing standardized prediction models like the Acute Physiology and Chronic Health Evaluation (APACHE) score, institutions can benchmark their observed outcomes against expected values by a prediction model [7, 8]. Discrepancies between predicted and actual outcomes can prompt investigations into best practices at high-performing centres, fostering a culture of continuous quality improvement in clinical toxicology, which is currently lacking.

Conclusion

Predicting outcomes in poisoned patients is a multifaceted process with far-reaching implications for patient care, resource management, treatment efficacy, and quality improvement initiatives. By leveraging predictive models and benchmarking practices, healthcare providers can enhance decision-making, optimize resource allocation, and ultimately improve patient outcomes in the field of clinical toxicology.

What to predict?

The exact prevalence of intoxications remains unknown; however, exposure to drugs and chemicals poses a significant global hazard [9]. Any individual, regardless of location or time, can encounter exogenous chemicals that may adversely affect their physiology and anatomy. Virtually any substance can be toxic when present in sufficient quantities. Individuals are routinely exposed to chemical hazards from various sources, such as household products, agricultural and industrial chemicals, medications, illegal drugs, and potentially even chemical terrorism [10].

While chemical exposure can have detrimental effects, most instances of exposure are minimal and often inconsequential. Seeking medical assistance following exposure to exogenous chemicals is typically rare and limited to a small percentage of individuals [11–13].

Yet, chemical exposure and poisoning continue to be prevalent reasons prompting patients to seek urgent medical care in hospital emergency departments [14–16]. The incidence of these exposures varies significantly between countries, influenced by local poisoning trends and disparities within healthcare systems. Globally, mortality rates from poisoning are relatively low, standing at approximately 1.1 per 100,000 inhabitants and showing a gradual decline. However, substantial variations exist among countries. For instance, in the United States (US), the death rate from unintentional poisoning is reported at 0.5 per 100,000 inhabitants. Despite this seemingly low rate, the overall mortality is steadily increasing due to the opioid crisis, which disproportionately impacts certain states within the US [17]. It is noteworthy that while mortality remains a rare outcome of acute poisoning in the Western World, it may not be the most critical outcome to predict due to rarity.

Predicting whether a poisoned patient needs (further) treatment or even admission to the hospital is one of the most difficult decisions a clinician needs to make. The prediction of the course of intoxication often lacks crucial information, leaving physicians with a sense of uncertainty in treating and advising patients. A significant source of this uncertainty stems from patients' limited awareness of the specific chemical(s) causing their symptoms, making a targeted approach challenging [18]. Furthermore, patients may withhold information about potential substances due to shame or fear of consequences, particularly in cases involving illegal drug use.

Adding to the complexity, patients and physicians frequently lack knowledge of the exposure dose, onset time, and potential interactions, further complicating the prediction of symptom progression. Without clarity on factors like the maximum concentration (Cmax) and time to maximum concentration (Tmax) of the drug and its metabolites, physicians often opt for a cautious monitoring approach. Patients are commonly placed in observation wards until the pharmacodynamic effects have diminished, leading to extended observation periods and unnecessary healthcare utilization and costs [19, 20].

Therefore, a key objective of a predictive model is to determine the necessity for ICU admission or hospital observation, aiming to streamline patient care, optimize resource allocation, and minimize healthcare expenses while ensuring timely and appropriate interventions [21].

Predicting the requirement for admission to an intensive care unit

In a pilot study conducted at a single centre, we evaluated the necessity for intensive treatment among a cohort from an emergency department [19]. Our criteria for 'justified treatment' encompassed interventions such as cardiopulmonary resuscitation, mechanical ventilation, haemodialysis, temperature management (cooling or warming), and gastrointestinal decontamination measures. Surprisingly, a quarter of hospitalized patients retrospectively did not require any treatment, highlighting potential inefficiencies in care delivery. The remaining patients underwent various therapeutic procedures, including the administration of isotonic crystalloids either continuously exceeding 100 mL/h or as a bolus exceeding 250 mL over 30 min.

In hindsight, those patients who did not necessitate treatment could have been promptly discharged from the emergency department, optimizing resource utilization and patient flow. However, the complexity arises from the challenge faced by physicians in making informed decisions when essential information may be lacking at that point of care. Enhancing decision-making processes through improved data availability and predictive tools can aid healthcare providers in determining the most appropriate course of action, leading to more efficient and tailored patient care.

To aid in the decision-making process, we developed a bedside model, which utilizes easily accessible variables during presentation to the emergency department to predict the requirement for ICU admission [21]. From a sample of more than 400,000 ICU patients, we selected only the patients who were intoxicated and directly transferred from the emergency department to the ICU, resulting in a cohort of 9,677 intoxicated individuals.

We defined 'justifiable ICU care' as instances involving mechanical ventilation within the initial 24 hours of ICU admission, the requirement for vasopressors within the first 24 h of admission, or mortality during the current hospital stay. While these criteria guided our assessment, we encountered scenarios in which patients had valid reasons for ICU admission, such as those who had undergone cardiopulmonary resuscitation before ICU transfer which necessitated care for sedation and temperature regulation. In such cases when ICU admission was unequivocally warranted, predictive modelling for admission necessity was unnecessary, and these patients were excluded from our study.

The likelihood of specific determinants being linked to a genuine requirement for ICU admission was assessed using a generalized linear mixed-effect model. The beta values covariates of the determinants were converted into a point system applicable at the bedside [22]. It appeared that the factors that most strongly associated with the requirement for ICU treatment were being 65 years old or older, having a Glasgow Coma Scale (GCS) of less than 6, and having certain co-morbidities such as dysrhythmias and chronic respiratory insufficiency (e.g., the need for supplementary oxygen at home). This retrospective model showed that if a patient scores 6 points or fewer, the chances of requiring ICU treatment are minimal. When we applied the model to a subset of patients (the validation cohort) from the same 9,677 patients, the model had a high negative predictive value of 97.8%. This result indicates that the model could precisely identify patients who did not require ICU treatment in 97.8% of cases. Nonetheless, in addition to the excellent overall discrimination in recognizing patients not needing ICU treatment, the model also needs good calibration. This means that the model performs equally well in predicting ICU requirements among patients with low and high predicted needs for ICU treatment. The calibration of such models is usually quite adequate when tested within the identical patient cohort as its development. However, its performance may not be as effective in varying groups of patients or healthcare systems. To test this, we needed external calibration or external validity testing [23].

Indeed, the 'ICU requirement score' was assessed in German and French cohorts, displaying similar negative predictive values for identifying patients who did not require ICU care, as observed in the original derivation cohort [24–26]. Nonetheless, it is important to externally validate the ICU requirement score on emergency department populations from various countries to determine its efficacy. In such an international prospective study, it would even be possible to incorporate other variables into the model to improve its discernment. However, a model based on more variables might have a better goodness-of-fit or better discrimination, but it might be more difficult to use at the bedside.

Two well-performed research studies in Korean emergency department patients showed that a more detailed model was associated with mortality rates with high accuracy (discrimination) [27, 28]. The factors closely linked with mortality, however, were essentially identical to those in the ICU requirement score. The analyzed factors comprised age, gender, exposure to particular xenobiotics (e.g., pesticides, benzodiazepines, paraquat), and physical anomalies observed upon arrival at the emergency department (e.g., blood pressure, heart rate, and respiration rate).

Enhancing prediction models for improved patient care

Look at the past: the patient's trajectory

If we look at the ICU requirement score, the Korean models, and many other prediction models, we see that many of the variables associated with the outcome are basically fixed variables, like age and co-morbidities. They are 'fixed' because we cannot influence them with our treatments. Patients cannot be made younger, and co-morbidities are often progressive over time rather than amenable to interventions. Therefore, the patient's resilience and chances of long-term survival in the ICU rely on their past medical history and the deterioration of organ function over time (i.e., co-morbidities). To achieve this, it is crucial to scrutinize a patient's medical history, as was illustrated by the ICU requirement score and the Korean study [29]. An aged person with several concurrent health conditions may struggle much more to deal with the sudden stress triggered by intoxication in comparison to a younger individual who has no organ damage.

Look to the future: what information do we need?

Looking ahead, it is crucial to address the challenge of underreporting in cases of xenobiotic chemical exposure, in which a significant number of individuals do not seek medical assistance, leading to an obscured understanding of poisoning incidence. In many middle- to high-income countries, the presence of poison centres offers a valuable resource for both the general public and healthcare professionals, providing essential guidance on managing potential intoxications. By leveraging these poison centres there is an opportunity to better ascertain the true prevalence of severe poisonings.

However, it is important to recognize that poison centres primarily assist individuals who actively seek help, representing only a fraction of the population potentially exposed to xenobiotic chemicals–specifically those who are cognizant of their exposure or experiencing symptoms. As a result, the phone calls received by poison centres offer only a glimpse into the broader issue at hand. Moving forward, efforts should focus on enhancing awareness and accessibility to poison centre services, promoting proactive engagement from both the public and healthcare providers to ensure comprehensive data collection and a more accurate representation of poisoning incidents within communities. By bridging this gap, we can improve surveillance, response mechanisms, and ultimately enhance public health outcomes related to chemical exposures and poisonings.

Supplementary data on the prevalence of intoxication can be derived from hospital and emergency department admission records. While administrative data may not encompass all xenobiotic chemicals due to limitations in the admission thesaurus, it remains a valuable source for understanding the frequency and severity of intoxications. It is essential to highlight that only admissions with a formal diagnosis are typically documented as reasons for admission, potentially underrepresenting the true scope of intoxication cases.

Moreover, it is critical to acknowledge that many instances of intoxication manifest with atypical signs and symptoms that can easily evade detection [29]. Particularly concerning are iatrogenic poisonings, which may go unnoticed even by seasoned healthcare professionals, leading to avoidable fatalities [30, 31].

To bridge the existing knowledge gap, establishing mandatory national and global databases to systematically document all cases of chemical-induced intoxications, akin to the surveillance of contagious infections, is imperative. However,

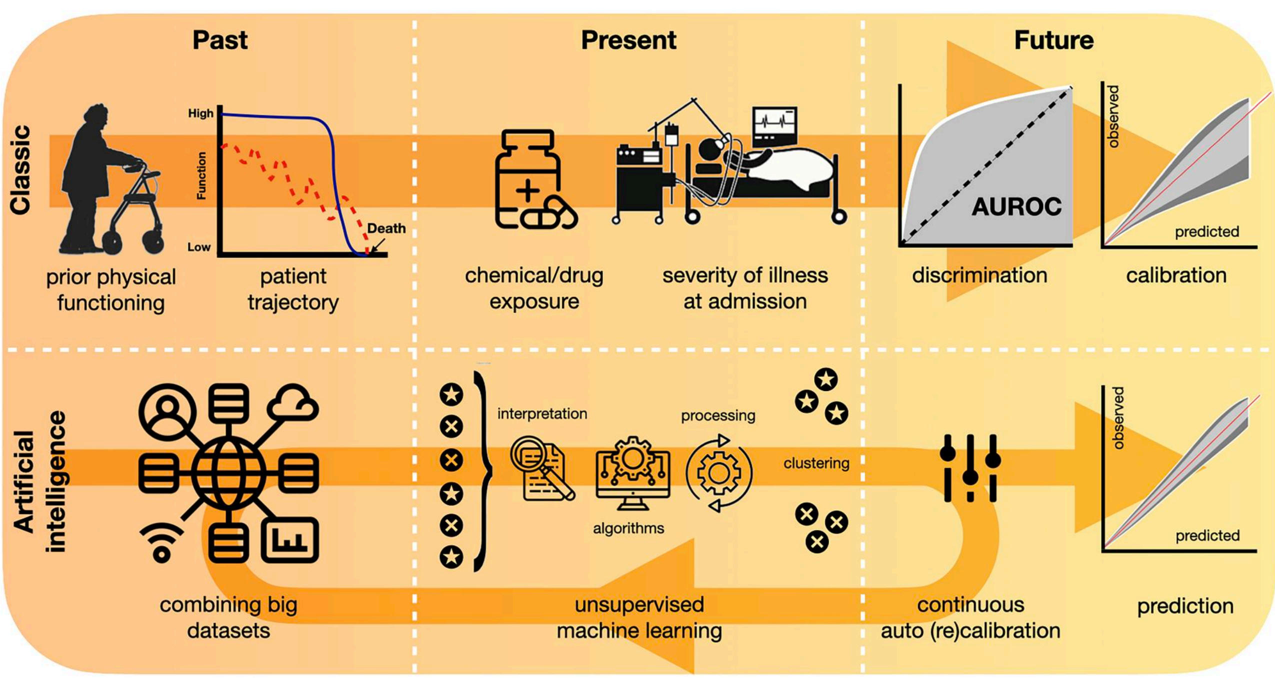

Figure 1. Traditional prognostic models traditionally focused on historical variables projected into the future. Key factors highly correlated with the desired outcome were integrated into a prognostic model using a multivariate regression approach. Subsequently, the model underwent rigorous evaluation for discrimination, calibration, and external validation. In cases of model inadequacy, extensive revisions were necessary. In contrast, modern prognostic models leverage unstructured, extensive datasets, commonly known as 'big data', to identify associations linked to outcome measures through machine learning clustering. These models adapt dynamically to incorporate new data, ensuring optimal discrimination and calibration for enhanced predictive accuracy. This agile approach allows for continuous refinement and adaptation, enabling more robust and responsive prognostic modelling in clinical practice. AUROC = Area under the receiver operator characteristic curve.

the comprehensive collection of such data poses significant challenges. A more feasible strategy involves integrating information from various sources, including poison centres, emergency departments, hospital admissions, administrative records, pharmacy registries, and other relevant sources. This integrated approach would facilitate the identification of meaningful temporal patterns and trends in intoxication incidents.

Presently, the amalgamation of data from diverse sources is hindered by the sheer volume of information and concerns surrounding data privacy. Overcoming these obstacles requires innovative solutions. Future advancements in information technology, particularly artificial intelligence and machine learning, hold promise in addressing the limitations of current toxicology databases. By leveraging these technologies to analyze vast datasets, we can enhance data integration, streamline surveillance efforts, and extract valuable insights to improve the prevention, management, and response to chemical intoxications on a broader scale.

Due to our limited ability to manually process large quantities of data, computers are essential for accurate calculations. Machine learning plays a critical role in simplifying our lives, even in the creation of predictive models, which possibly rely on massive amounts of data (called 'big data') [32]. Supervised learning is a subdivision of artificial intelligence and machine learning that employs labelled datasets to train algorithms for data classification or prediction. One of the innovative features of machine learning is 'incremental learning' (i.e., the ability of a computer to update the model in real time as soon as new data is received) (Figure 1).

The volume of data aids in constructing a more reliable model that accurately predicts the output, which consequently influences the precision of the output. This notable feature of machine learning algorithms to handle big data enables them to automatically explore the data, create models and predict the necessary output. This way, we can train machine learning algorithms and apply them to new data. Unsupervised learning algorithms excel at more intricate processing tasks, such as organizing vast datasets into clusters. Unsupervised learning techniques can be valuable in revealing hidden patterns within data, aiding in the identification of relevant data features. Within datasets of poisoned patients, these methods can enable the recognition of clusters of similar phenotypic traits or shared pathophysiological mechanisms that lead to comparable treatment options.

Conclusions

The future holds great promise for clinical toxicologists when we advocate the development of comprehensive databases that can harness big data and utilize machine learning systems to analyze patient trajectories. By categorizing these trajectories into treatable trait groups, we can significantly influence the direction of clinical toxicology. While predictions are difficult, particularly about the future (Danish proverb), the outlook for prognostication in clinical toxicology is indeed optimistic. Embracing innovative technologies and data-driven approaches will undoubtedly revolutionize how we understand, predict, and manage toxicological outcomes, paving the way for more effective interventions and improved patient care in the field of clinical toxicology.

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