ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2022 September 9; 11(5): 311-341

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

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INDEXING/ABSTRACTING

The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Li-Li Wang*.

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Hua-Dong Wang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
September 9, 2022

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World Journal of Critical Care Medicine

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World J Crit Care Med 2022 September 9; 11(5): 311-316

DOI: 10.5492/wjccm.v11.i5.311

ISSN 2220-3141 (online)

EDITORIAL

Data science in the intensive care unit

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chavan RP, India; Wong YP, Malaysia

Received: April 11, 2022
Peer-review started: April 11, 2022
First decision: April 28, 2022
Revised: May 3, 2022
Accepted: July 16, 2022
Article in press: July 16, 2022
Published online: September 9, 2022

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Abstract

In this editorial, we comment on the current development and deployment of data science in intensive care units (ICUs). Data in ICUs can be classified into qualitative and quantitative data with different technologies needed to translate and interpret them. Data science, in the form of artificial intelligence (AI), should find the right interaction between physicians, data and algorithm. For individual patients and physicians, sepsis and mechanical ventilation have been two important aspects where AI has been extensively studied. However, major risks of bias, lack of generalizability and poor clinical values remain. AI deployment in the ICUs should be emphasized more to facilitate AI development. For ICU management, AI has a huge potential in transforming resource allocation. The coronavirus disease 2019 pandemic has given opportunities to establish such systems which should be investigated further. Ethical concerns must be addressed when designing such AI.

Key Words: Artificial intelligence; COVID-19; Data science; Intensive care units; Interaction

Core Tip: Data in intensive care units (ICUs) can be classified into qualitative and quantitative data with different technologies needed to translate and interpret them. Data science, in the form of artificial intelligence (AI), should find the right interaction between physicians, data and algorithm to maximize the utility. AI deployment in the ICUs should be emphasized more to facilitate AI development. Individual-level applications such as disease prediction, and ICU-level potentials such as resource allocation are both of paramount importance.

Citation: Luo MH, Huang DL, Luo JC, Su Y, Li JK, Tu GW, Luo Z. Data science in the intensive care unit. *World J Crit Care Med* 2022; 11(5): 311-316
URL: https://www.wjgnet.com/2220-3141/full/v11/i5/311.htm
DOI: https://dx.doi.org/10.5492/wjccm.v11.i5.311

INTRODUCTION

The intensive care unit (ICU) is a data-rich setting where the right decision can mean the difference between life and death. This gives the ICU the perfect opportunity to explore the impact of data science combined with artificial intelligence (AI) to maximize the utility and benefits. However, challenges remain because the interpretation of an incredibly huge amount of data is still a black hole with many questions unanswered. Although many models have been created, their clinical applications are limited. Attention is mostly paid to individual-level decision making such as diagnosing and predicting the prognosis of a specific disease, while potentials at a more macroscopic level such as ICU resource allocation, are largely omitted.

Generally speaking, data in the ICU can be classified into qualitative and quantitative data. Qualitative data include graphical data such as waves on the ventilation machine, and radiological data such as x-rays or computed tomography scans. Such data need to be translated first before being further calculated. Recently, we have seen a substantial number of researches focusing on such a translation process[1-4]. Quantitative data in the form of numbers such as physiological parameters, laboratory results, dosage of medication and ICU bed capacity, are common to intensivists. This kind of data has the advantage of being readily available for statistical analyses without the necessity for further processing into means that are more accessible.

The key to making full use of data in ICUs is to find the right interaction between three roles: physicians, data and algorithm (Figure 1). Physicians need to ask the right clinical question which points out the direction of the research and the data we should pay attention to. The data should be collected and interpreted in a way that can be processed by current software. The collection of data should follow certain statistical rules and avoid bias as much as possible. The algorithm can be built to find patterns based on a large quantity of data and these patterns should target clinical questions raised by physicians.

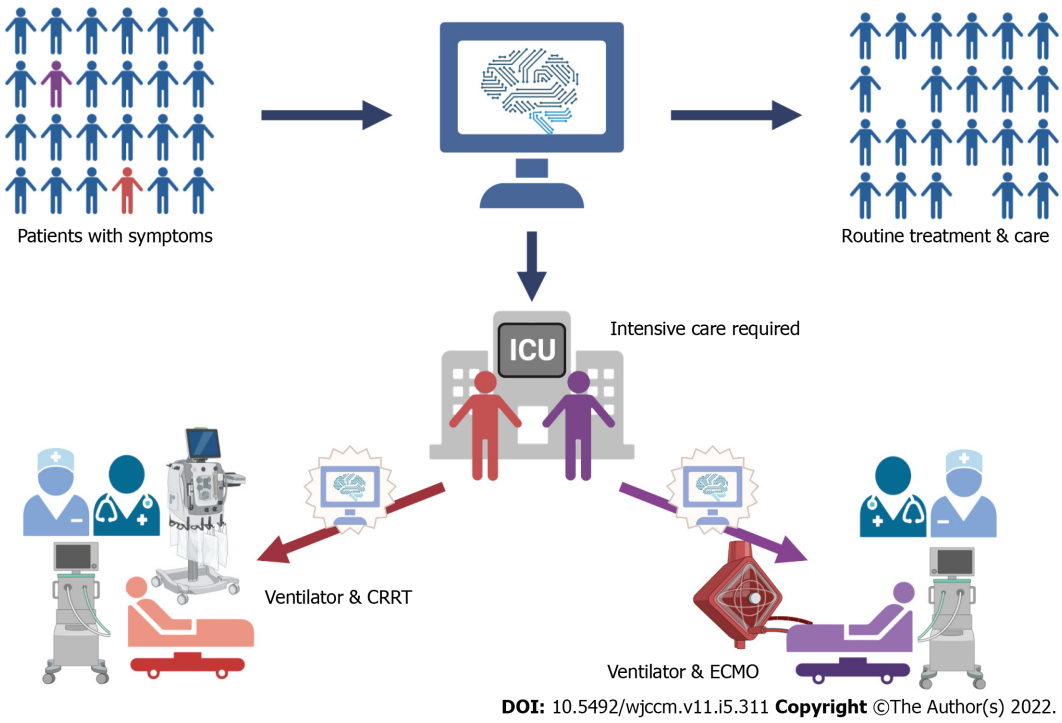
DECISION MAKING AND PREDICTIVE MODELS

Two examples where predictive models are supported by AI in decision making in ICUs are sepsis and mechanical ventilation. Sepsis is a leading cause of morbidity and mortality in critically ill patients. AI models have been studied in different stages such as the detection, prediction, risk stratification and management of sepsis. Goh *et al*[5] developed an algorithm with independent clinical notes and achieved high predictive accuracy 12 h before the onset of sepsis (Area under curve 0.94). It also has great potential for improving the early identification of patients who may benefit from the administration of antibiotics. Moreover, it can discover new phenotypes for sepsis potentially transforming sepsis treatment and offering a more tailored strategy for patients with sepsis[6], such as the use of glucocorticoids[7]. Clinicians hold a positive view in letting AI take a more active role when managing patients with sepsis[8].

Mechanical ventilation is another common situation in ICUs. Machine learning can predict the need for intubation in critically ill patients using commonly collected bedside clinical parameters and laboratory results[9]. AI has the potential to identify treatable phenotypes, optimize ventilation strategies and provide clinical decision support for patients who require mechanical ventilation[10]. Zhao *et al*[11] also created a model for predicting extubation failure in ICUs with an AUROC of 0.835 and 0.803, respectively, for internal and external validation.

Such an exciting trend should be viewed with caution. Current AI prediction models to diagnose sepsis are at a major risk of bias when the diagnostic criteria vary. The generalizability of these models is poor due to overfitting and the lack of standardized protocols. Similar conditions occur for mechanical ventilation. AI applied to mechanical ventilation has limited external validation and model calibration with a substantial risk of bias, significant gaps in reporting and poor code and data availability[10].

Mamdani and Slutsky summarized three themes in applied AI in medicine: (1) Enabling data; (2) AI development; and (3) AI deployment. We believe that AI development and AI deployment should be combined to revise current models and offer tangible benefits derived from current researches. A vast majority of developed ICU-AI models remain within the testing and prototyping environment and only a handful have been actually evaluated in clinical practice[12] which implies the lack of enough evidence to support the clinical values of published models. Focusing more on AI deployment in the form of



DOI: 10.5492/wjccm.v11.i5.311 **Copyright** ©The Author(s) 2022.

Figure 1 Interaction between artificial intelligence development and artificial intelligence deployment. Artificial intelligence (AI) development and AI deployment should be combined to revise current models and offer tangible benefits derived from current researches. AI development should find the right interaction between three roles: physicians, data and algorithm. AI deployment in the form of prospective randomized controlled trials can facilitate published models to generate bedside merits and evaluate whether major biases exist. The results from deployment testing can, in turn, offer insights into the development and modify the substandard algorithm. CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation.

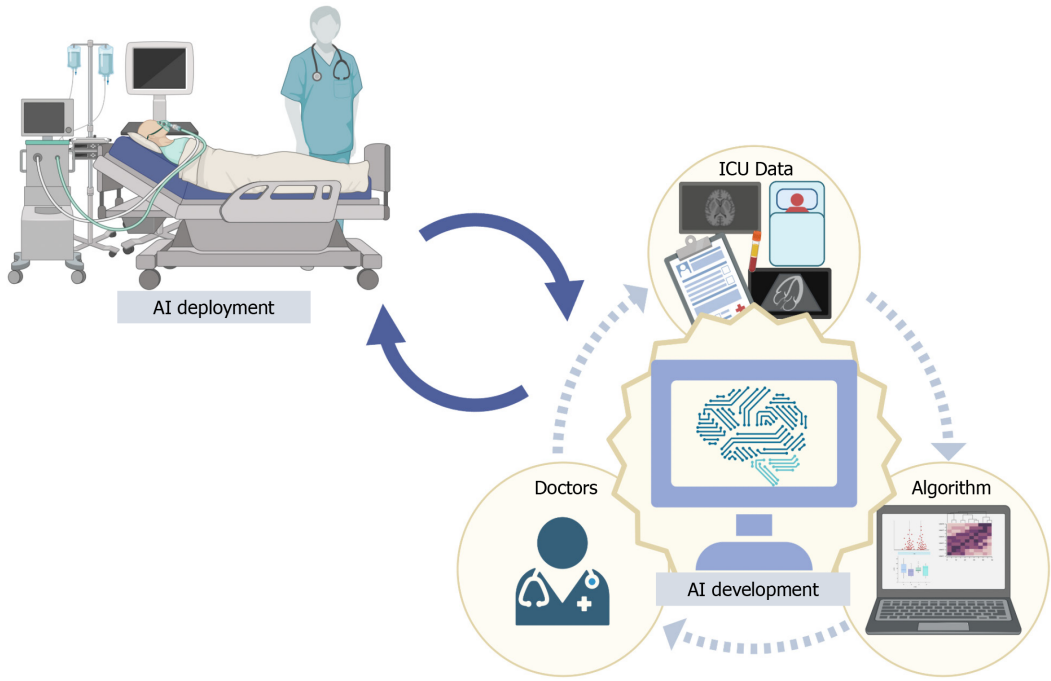
prospective randomized controlled trials would not only facilitate published models to generate bedside merits but also test and evaluate whether major biases exist and clinical needs can be met in a satisfactory way. The results from deployment testing can, in turn, offer insights into the development and modify the substandard algorithm (Figure 1).

RESOURCE ALLOCATION

Machine learning and algorithm have been widely used to manage resource allocation. Machine learning has been studied for predictive scheduling and resource allocation in large-scale manufacturing systems and resource allocation strategies in vehicular networks using machine learning have been extensively explored[13,14]. These settings are similar to ICUs in that both need to capture the value from big data processing and extract useful insights to optimize production and protect resources.

However, in the realm of critical care, where resource can be scarce due to factors such as bed capacity, the applications of machine learning has just shown a glimpse of light (Figure 2). Over the past 2 years, these applications in the context of the coronavirus disease 2019 (COVID-19) ICUs offered more chances to lay emphasis on resource allocation. Cheng *et al*[15] used machine learning to predict ICU transfer in hospitalized patients with COVID-19 and concluded that it could improve the management of hospital resources and patient-throughput planning. Similar principles were used to predict the use of ICU resources, such as mechanical ventilation, during the COVID-19 pandemic in Denmark[15]. At a healthcare system level, the National Health Service (NHS) in the United Kingdom started trials of a machine-learning system designed to help hospitals in England anticipate the demand on resources caused by COVID-19. COVID-19 Capacity Planning and Analysis System, a machine learning-based system for hospital resource planning, was subsequently developed that could be deployed at individual hospitals and across regions in the United Kingdom in coordination with NHS Digital[16].

Such models can take the application of AI in ICUs to another level. Although its insight into disease prediction, diagnosis and management is extremely important, it gives the chance to make the most use of resources, especially in ICUs where demand and supply frequently mismatch. Prediction in interventions such as mechanical ventilation would mean that the management groups can foresee changes and mobilize resource, such as equipment and staff, to cope with such demands in advance and this is a positive factor for patient outcomes.



DOI: 10.5492/wjccm.v11.i5.311

Figure 2 Resource allocation in the intensive care units. The applications of machine learning can target patients in need of intensive care units (ICUs) and predict the use of ICU resources. Machine learning can predict ICU transfer in hospitalized patients and predict the use of ICU resources, such as mechanical ventilation. It gives the chance to make the most use of resources, especially in ICUs where demand and supply frequently mismatch. Prediction in interventions, such as mechanical ventilation, would mean that the management groups can foresee changes and mobilize resource, such as equipment and staff, to cope with such demands in advance which is a positive factor for patient outcomes. AI: Artificial intelligence.

Besides efficiency, another aspect that we must pay attention to is how to answer the ethical questions embodied in resource allocation to achieve a healthcare system that values equity and sustainability. This implies that ethical considerations must be included and certain ethical principles must be followed when designing the algorithm. Recently, a set of new studies focused on the ethics of healthcare resource allocation, drawing attentions to patient need, prognosis, equal treatment and cost-effectiveness[17]. Also, numerous comments were made during the COVID-19 pandemic that AI should stick to the ethical standards[18-20]. In a broader setting, the so-called algorithmic fairness highlights specific opportunities where machine learning and public and population health may synergize to achieve health equity[21]. Challenges remain as what ethical principles matter and what priority should be given to each ethical principle and coding them into an algorithm has not been intensively experimented.

CONCLUSION

AI has become more prevalent in the ICUs. Different kinds of data are collected constantly and should be interpreted in an accurate fashion. The key to maximizing AI in the ICU is to find the right balance between data, algorithms and physicians to ensure that the technical, computational and clinical needs are targeted.

For individuals, sepsis and mechanical ventilation have been two important aspects where AI has been extensively studied. However, major risks of bias, lack of generalizability and poor clinical values imply that AI is far from perfect. AI deployment in ICUs should be more emphasized to facilitate AI development.

More importantly, AI has huge potential in transforming resource allocation in ICUs. The COVID-19 pandemic has given some opportunities to establish such systems and more should be investigated. Ethical concerns must be addressed when designing such AI.

FOOTNOTES

Author contributions: Luo MH drafted the manuscript; Tu GW and Luo Z substantively revised it; All authors participated in the conception and design of the work.

Conflict-of-interest statement: All authors have no conflicts of interest to declare.

Country/Territory of origin: China

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S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL

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World Journal of Critical Care Medicine

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World J Crit Care Med 2022 September 9; 11(5): 317-329

DOI: 10.5492/wjccm.v11.i5.317

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Study

Prediction of hospital mortality in intensive care unit patients from clinical and laboratory data: A machine learning approach

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cabezuelo AS, Spain

Received: June 22, 2021
Peer-review started: June 22, 2021
First decision: July 31, 2021
Revised: August 13, 2021
Accepted: July 5, 2022
Article in press: July 5, 2022
Published online: September 9, 2022

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Abstract

BACKGROUND

Intensive care unit (ICU) patients demand continuous monitoring of several clinical and laboratory parameters that directly influence their medical progress and the staff's decision-making. Those data are vital in the assistance of these patients, being already used by several scoring systems. In this context, machine learning approaches have been used for medical predictions based on clinical data, which includes patient outcomes.

AIM

To develop a binary classifier for the outcome of death in ICU patients based on clinical and laboratory parameters, a set formed by 1087 instances and 50 variables from ICU patients admitted to the emergency department was obtained in the "WiDS (Women in Data Science) Datathon 2020: ICU Mortality Prediction" dataset.

METHODS

For categorical variables, frequencies and risk ratios were calculated. Numerical variables were computed as means and standard deviations and Mann-Whitney *U* tests were performed. We then divided the data into a training (80%) and test (20%) set. The training set was used to train a predictive model based on the Random Forest algorithm and the test set was used to evaluate the predictive effectiveness of the model.

RESULTS

A statistically significant association was identified between need for intubation, as well predominant systemic cardiovascular involvement, and hospital death. A number of the numerical variables analyzed (for instance Glasgow Coma Score

punctuations, mean arterial pressure, temperature, pH, and lactate, creatinine, albumin and bilirubin values) were also significantly associated with death outcome. The proposed binary Random Forest classifier obtained on the test set (n = 218) had an accuracy of 80.28%, sensitivity of 81.82%, specificity of 79.43%, positive predictive value of 73.26%, negative predictive value of 84.85%, F1 score of 0.74, and area under the curve score of 0.85. The predictive variables of the greatest importance were the maximum and minimum lactate values, adding up to a predictive importance of 15.54%.

CONCLUSION

We demonstrated the efficacy of a Random Forest machine learning algorithm for handling clinical and laboratory data from patients under intensive monitoring. Therefore, we endorse the emerging notion that machine learning has great potential to provide us support to critically question existing methodologies, allowing improvements that reduce mortality.

Key Words: Hospital mortality; Machine learning; Patient outcome assessment; Routinely collected health data; Intensive care units; Critical care outcomes

Core Tip: Considering the critical nature of patients admitted to intensive care units (ICUs), this study seeks to analyze clinical and laboratory data using a machine learning model based on a Random Forest algorithm. Consequently, we developed a binary classifier that forecasts death outcome, achieving a relevant area under the curve value of 0.85 and identifying the variables that contributed the most to the prediction. With this, we aim to contribute to the improvement and methodological advancement in the development of clinically relevant machine learning tools, seeking to make medical practice decisions more accurate and reduce mortality in ICU patients.

Citation: Caires Silveira E, Mattos Pretti S, Santos BA, Santos Corrêa CF, Madureira Silva L, Freire de Melo F. Prediction of hospital mortality in intensive care unit patients from clinical and laboratory data: A machine learning approach. *World J Crit Care Med* 2022; 11(5): 317-329
URL: https://www.wjgnet.com/2220-3141/full/v11/i5/317.htm
DOI: https://dx.doi.org/10.5492/wjccm.v11.i5.317

INTRODUCTION

The intensive care unit (ICU) is the section of the hospital responsible for monitoring acute patients, and it relies on specialized multidisciplinary staff and high-technology equipment to ensure the best support for these patients, who are usually unstable and at high risk of death. These patients demand continuous monitoring of the most diverse clinical and laboratory parameters that directly influence their medical progress and the staff's decision-making. Lactate levels obtained from arterial blood samples, for example, may indicate the levels and severity of tissue hypoxia[1]. The elevation in serum lactate levels (hyperlactatemia) is associated with increased mortality[2,3]. Another important parameter in critically ill patients is the prothrombin time expressed in international normalized ratio (INR), which reveals abnormalities in the coagulation status[4]. This parameter is also associated with an increased mortality when at altered levels. Besides these, many other laboratory and clinical data like temperature, oxygen and carbon dioxide pressure, systolic and diastolic pressure, motor, ocular, and verbal responses, among others, require team supervision since they are all related in some way to the severity of these ill patients[5].

These data are so vital in the assistance of these patients that they are already used by several scoring systems, including the Acute Physiology and Chronic Health Evaluation (APACHE) and the Simplified Acute Physiology Score (SAPS), which are designed to assess and predict the patient's prognosis and allow for appropriate interventions[6]. The APACHE score, for example, which has been widely used since its creation in the 1980s and has been undergoing updates ever since, relies on the use of parameters evaluated in three major groups: Demographic characteristics, comorbidities, and physiological measures. From these data, numerical weights are assigned to each one and then summed to assign a severity classification and predict outcomes[7].

Machine learning may be understood as a scientific discipline by which a computer system is enabled to cross-reference numerous data in order to build statistical prediction models through pattern recognition[8]. To reach this pattern perception capability, it is essential during the use of the supervised

machine learning approach to separate the data subsets for training and for testing. The training data are presented to the algorithm in order to create the model, and then the test data is also presented after the creation of the model in order to simulate this model's prediction and evaluate its performance. The machine learning approach is already used for medical predictions based on clinical data, which includes patient outcome. Heo *et al*[9] used it to predict the long-term outcome of patients who suffered an ischemic stroke. In another study, Lynch *et al*[10] sought a survival prediction of lung cancer patients using machine learning by providing a series of patient data such as age, tumor size, type of intervention, and more.

The use of machine learning has been consolidated as an alternative for the development of predictive models of mortality in the critical care setting. An example is the retrospective study by Liu *et al*[11], who developed a logistic model of the death risk grade in patients with pulmonary tuberculosis using data from patients admitted to ICUs in three hospitals. In this multivariate analysis study, where the sensitivity was 83.3% and specificity was 73.1%, the Apache II score, C-reactive protein levels, albumin levels, and pressure of oxygen in arterial blood (PaO_2) were considered the main factors influencing the outcome. However, a registered limitation was the small dataset utilized.

The limiting matter caused by the database used in machine learning predictive models was also observed in the study by Hou *et al*[12], who developed a model regarding 30-d mortality in patients who fit the Third International Consensus Definitions for Sepsis (Sepsis-3). This paper used a public database Medical Information Mart for Intensive Care III (MIMIC III) from a single-center critical care database. Another study that also relates the development of a predictive machine learning model in the context of patients with sepsis is the one proposed by Nemati *et al*[13] that, in addition to using the aforementioned MIMIC III, also relied on ICU admission data from two hospital centers. In this study, as well as in the two previously mentioned, the potentialuses of this tool in the early identification of severity of cases and the possibility of making fundamental decisions to the positive outcome for patients was observed.

In addition, more recently, in light of the advent of the severe acute respiratory syndrome coronavirus 2 pandemic, the application of these predictive models using machine learning technology have been employed on various grounds, such as for risk of critical coronavirus disease 2019 (COVID-19)[14], need for ICU transfer, and the prognosis of intensive care COVID-19 patients[15,16]. The latter one was associated with eight main component factors, namely: Lymphocyte percentage, prothrombin time, lactate dehydrogenase, total bilirubin, eosinophil percentage, creatinine, and neutrophil percentage. And although it also emphasized the difficulties of small databases, they pointed out the significance of this approach in critical patients with a panel of such complicated parameters.

Understanding a clinical setting as complex and full of variables as the ICU, identifying existing patterns, and enabling outcome prediction is a valuable tool for the improvement of health assistance to these patients. Therefore, the aim of the current paper is to develop a predictive model for the outcome of death in ICU patients based on clinical and laboratory parameters using a binary classifier, with predicted outcome consisting of in-hospital death and discharge.

MATERIALS AND METHODS

Data acquisition

We used anonymized retrospective data from ICU patients admitted to the emergency department to build a predictive model geared towards predicting death outcomes in these patients. For this purpose, a dataset used in the study was created from the larger "WiDS (Women in Data Science) Datathon 2020: ICU Mortality Prediction" dataset[17], which presents clinical and laboratory data pertaining to the first 24 h of ICU patient admission. The criteria for inclusion of instances (*i.e.*, patients) in the study dataset were: (1) ICU admission and emergency department admission; and (2) Completeness (*i.e.*, absence of missing data) with respect to the variables of interest. Since all the data were obtained from a public and anonymized dataset[16], it was not necessary to submit this study to the ethics committee, being in accordance with all the established precepts by the Committee on Publication Ethics.

Data preprocessing and exploratory data analysis

Aligned with the goal of building an interpretable predictive model from clinical and laboratory data, variables related to the clinical status of patients (such as vital signs, clinical score scores, blood counts, and biochemical test results) were prioritized in the definition of variables of interest - with exclusion of variables of this type only when redundant or when they represented the application of formulas instead of measured or scored values - to the detriment of anthropometric and demographic variables, with age being the only representative of this group of variables included. Additionally, factors referring to logistical aspects of hospitalization (such as source and type of admission and readmission status) were also not included among the variables of interest.

This way, a set formed by 1087 instances and 50 variables was obtained, of which 49 were assumed as predictive variables and 1 as predicted variable (outcome variable). The predictive numerical variables were: (1) Age; (2) Disease score; (3) Eye opening score on the Glasgow coma scale (GCS); (4) Heart rate;

(5) Hematocrit; (6) Mean arterial pressure; (7) Maximum albumin; (8) Maximum bilirubin; (9) Maximum blood urea nitrogen; (10) Maximum calcium; (11) Maximum creatinine; (12) Maximum diastolic blood pressure; (13) Maximum glucose; (14) Maximum HCO_3; (15) Maximum hemoglobin; (16) Maximum INR; (17) Maximum lactate; (18) Maximum platelets; (19) Maximum potassium; (20) Maximum sodium; (21) Minimum systolic blood pressure; (22) Maximum saturation of peripheral oxygen (SpO_2); (23) Maximum white blood cells (WBC); (24) Minimum albumin; (25) Minimum bilirubin; (26) Maximum blood urea nitrogen; (27) Minimum calcium; (28) Minimum creatinine; (29) Minimum diastolic blood pressure; (30) Minimum glucose; (31) Minimum HCO_3; (32) Minimum hemoglobin; (33) Minimum INR; (34) Minimum lactate; (35) Minimum platelets; (36) Minimum potassium; (37) Minimum sodium; (38) Minimum systolic blood pressure; (39) Minimum SpO_2; (40) Minimum WBC; (41) Motor response on the GCS; (42) Partial PaO_2; (43) Partial pressure of carbonic gas in arterial blood ($PaCO_2$); (44) pH; (45) Respiratory rate; (46) Temperature; and (47) Verbal response on the GCS. The predictive categorical variables were: (1) Need for intubation or not; and (2) Predominant systemic involvement. The outcome variable was the evolution or not with hospital death.

The disease score corresponded to the number of diseases present among the following conditions: (1) Acquired immunodeficiency syndrome; (2) Cirrhosis; (3) Diabetes; (4) Hepatic failure; (5) Immunosuppression; (6) Leukemia; (7) Lymphoma; and (8) Solid tumor. The categories of predominant systemic involvement considered were: (1) Cardiovascular involvement; (2) Gastrointestinal involvement; (3) Genitourinary involvement; (4) Hematological involvement; (5) Metabolic involvement; (6) Musculoskeletal/skin involvement; (7) Neurological involvement; (8) Respiratory involvement; (9) Sepsis; and (10) Trauma.

Initially, a descriptive and comparative analysis of the data was performed. The data were categorized according to the outcome variable. After that, the occurrence frequencies of each category for of categorical predictive variables and the means and standard deviations for all numerical predictive variables in both groups were computed. Finally, the differences for each variable between the groups were analyzed using the χ^2 test for risk ratios (for categorical variables) and the Mann-Whitney U test (for numerical variables). Since a decision tree ensemble algorithm was chosen to constitute our predictive model, it was not necessary to normalize or standardize the data, since tree partitioning algorithms are insensitive to scaling.

Machine learning algorithm selection

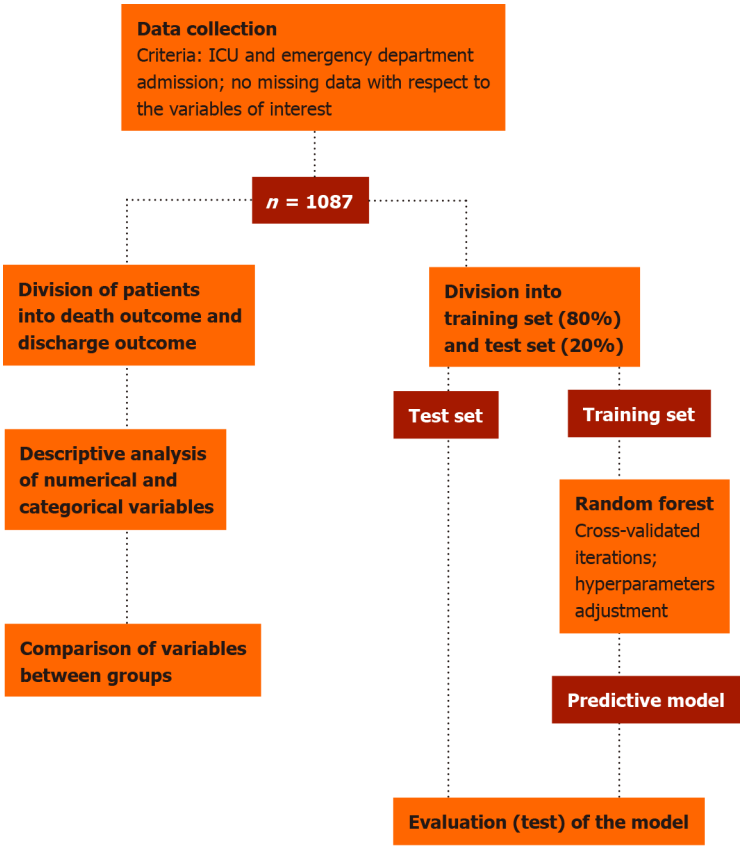
To perform our predictive analysis, we chose to build a Random Forest algorithm, a model consisting of an ensemble of randomized decision trees. As an extension of bootstrap aggregation (bagging) of decision trees, in Random Forest algorithms each individual model in the ensemble is employed to generate a prediction for a new sample, and these individual model predictions are averaged to give the forest's prediction, resulting in better performance than any single tree. By combining individual models, the ensemble model tends to be more flexible and efficient. Accordingly, random forests have been incredibly successful in a variety of classification and regression problems with clinical applications. Furthermore, the algorithm does not require any feature scaling since decision trees predictions are partitioning-based instead of distance-based.

Model training and evaluation

We then proceeded to the development of the predictive model for the outcome variable. The data were divided into a training set (80%) and a test set (20%). The training set was used to train a predictive model based on the Random Forest algorithm[18], implemented here through the Scikit-learn open source library[19]. The test set was used to evaluate the predictive effectiveness of the model. The metrics used for such evaluation were accuracy, sensitivity, specificity, area under the curve (AUC) score, positive predictive value, and negative predictive value. The adopted methodology is schematically summarized in Figure 1. Besides the predictive performance, the feature importance attributed by the model to each variable was also considered, which not only adds explainability to the model, but also potentially provides insights regarding the evaluation of critically ill patients and the factors associated with higher mortality in this clinical setting. All steps of statistical analysis and development of the predictive model were performed in Python (version 3.6.9) using SciPy and Scikit-learn libraries.

RESULTS

Data from 1087 ICU patients were analyzed and used in the construction of the predictive model, of which 388 evolved with hospital death, while the remaining 699 did not. With regard to the predictive variables categories - need or not of intubation and predominantly affected body system -, among the 388 patients who evolved with hospital death: 275 were intubated and 63 were not; 106 had sepsis as predominant systemic involvement, 18 respiratory involvement, 4 metabolic involvement, 154 cardiovascular involvement, 11 trauma, 16 neurological involvement, 25 gastrointestinal involvement, 2 genitourinary involvement, 1 musculoskeletal/skin involvement, and 1 hematological involvement. Among the 699 patients who did not progress to hospital death: 534 were intubated and 215 were not;



DOI: 10.5492/wjccm.v11.i5.317

Figure 1 Methodological design of the study. The proposed workflow encompasses selective collection of clinical, laboratorial and outcome data, splitting and pre-processing of the data, iterative training of the classificatory model, and finally evaluation of its performance. ICU: Intensive care unit.

206 had sepsis as predominant systemic involvement, 107 respiratory involvement, 79 metabolic involvement, 167 cardiovascular involvement, 38 trauma, 49 neurological involvement, 74 gastro-intestinalintestinal involvement, 17 genitourinary involvement, 9 musculoskeletal/skin involvement, and 3 hematological involvement. A statistically significant association was identified between need for intubation and hospital death (risk ratio = 1.5, $\chi^2 = 11.87$, $P < 0.001$), as well as between the predominant systemic cardiovascular involvement and hospital death compared to the musculoskeletal system/skin, which related to lower rate of hospital death (risk ratio = 4.80, $\chi^2 = 4.20$, $P = 0.04$). With regards to numerical predictive variables, their mean ± SD, and the respective comparison between both outcome groups (performed using the Mann-Whitney *U* test) are shown in Table 1.

The search for the best hyperparameters in our Random Forest model training was done using randomized search. In this way, 100 random combinations of hyperparameters were tested. Each combination was iterated 6 times, as a 6-fold validation scheme was adopted. In this scheme, the training set ($n = 869$) was split into 6 parts, and in each iteration a different part was used for validation. Ultimately, during training we performed 600 fits, obtaining the following hyperparameters: (1) Number of estimators = 213; (2) Maximum depth = 23; (3) Maximum leaf nodes = 24; (4) Minimum samples split = 5; (5) Class weights = 3.9; and (6) Bootstrap = true.

The model obtained accuracy of 80.28%, sensitivity of 81.82%, specificity of 79.43%, positive predictive value of 73.26%, negative predictive value of 84.85%, F1 score of 0.74, and AUC score of 0.85 on the test set ($n = 218$). The confusion matrix for the model is shown in Figure 2, and its receiver operating characteristic (ROC) curve is shown in Figure 3. The predictive variables with the greatest importance were the maximum and minimum lactate values, adding up to a predictive importance of 15.54%, followed by temperature (6.47%), motor punctuation in GCS (5.25%), maximum blood urea nitrogen (4.35%), and minimum WBC (3.31%). The percentage importance of the other variables in the prediction are listed in Table 2.

DISCUSSION

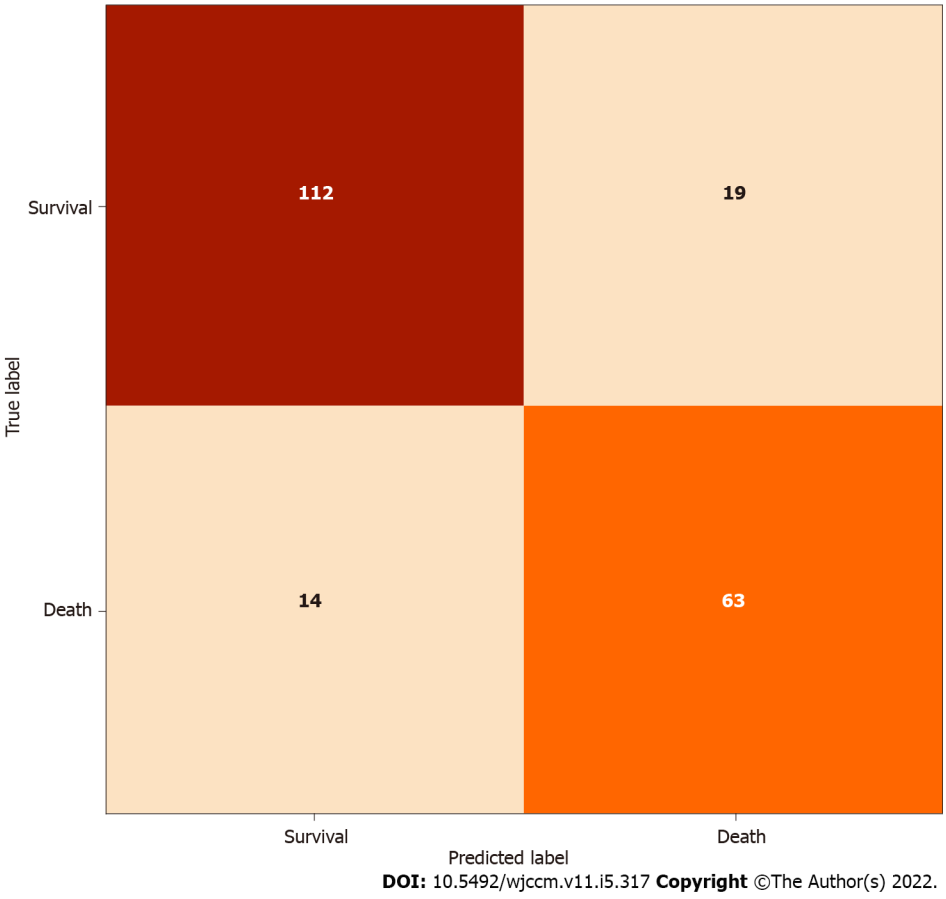
The presented predictive model, a Random Forest binary classifier, was able to predict in the test set the occurrence or not of hospital death with an accuracy of 80.28%, sensitivity of 81.82%, and specificity of

Table 1 Descriptive and univariate comparative analyses for numerical predictive variables according to outcome

Variable	mean ± SD		*U* value	*P* value
	Death outcome, *n* = 338	Survival outcome, *n* = 749		
Age	63.4 ± 15.7	60.1 ± 16.1	111072	< 0.001
Disease score	1.3 ± 0.8	1.2 ± 0.7	121505.5	0.110
Eye opening (GCS)	2.0 ± 1.2	2.5 ± 1.2	97325.0	< 0.001
Heart rate	114.3 ± 34.9	111.1 ± 31.1	117672.0	0.031
Hematocrit	31.7 ± 8.3	32.8 ± 7.3	116749.0	0.02
MAP	84.7 ± 53.9	87.4 ± 48.7	108432.0	< 0.001
Max albumin	2.7 ± 0.7	2.8 ± 0.6	109136.0	< 0.001
Max bilirubin	2.2 ± 3.8	1.2 ± 1.8	98589.5	< 0.001
Max BUN	40.0 ± 25.2	33.8 ± 24.5	102300.0	< 0.001
Max calcium	8.0 ± 0.9	8.1 ± 0.8	117155.0	0.024
Max creatinine	2.6 ± 2.0	2.0 ± 1.9	96278.5	< 0.001
Max DBP	92.0 ± 23.1	94.8 ± 21.5	116162.0	0.015
Max glucose	231.4 ± 113.0	210.1 ± 105.2	11090.0	< 0.001
Max HCO_3	21.0 ± 5.1	23.3 ± 4.8	94750.0	< 0.001
Max hemoglobin	11.7 ± 2.5	11.7 ± 2.3	124619.0	0.341
Max INR	2.1 ± 1.3	1.6 ± 0.8	83944.0	< 0.001
Max lactate	7.3 ± 5.5	3.2 ± 2.8	62255.5	< 0.001
Max platelets	189446.7 ± 98687.9	198186.9 ± 96842.7	120773.5	0.113
Max potassium	4.7 ± 0.9	4.5 ± 0.8	106603.0	< 0.001
Max sodium	142.1 ± 6.7	140.9 ± 5.4	113894.0	0.004
Max SBP	147.5 ± 29.3	151.1 ± 26.2	113747.5	0.004
Max SpO_2	99.6 ± 1.5	99.8 ± 0.6	119714.5	0.005
Max WBC	17442.9 ± 10269.3	15302 ± 8516	111218.5	0.001
Min albumin	2.5 ± 0.7	2.7 ± 0.6	101997.5	< 0.001
Min bilirubin	1.9 ± 3.3	1.1 ± 1.7	101177.5	< 0.001
Min BUN	34.2 ± 22.9	29.0 ± 21.0	106584.5	< 0.001
Min calcium	7.4 ± 0.9	7.7 ± 0.9	98668.5	< 0.001
Min creatinine	2.08 ± 1.7	1.6 ± 1.3	99935.0	< 0.001
Min glucose	104.6 ± 47.0	110.7 ± 38.1	111941.5	0.001
Min HCO_3	17.0 ± 5.5	20.6 ± 5.5	79747.5	< 0.001
Min hemoglobin	10.3 ± 2.7	10.8 ± 2.4	111370.0	0.001
Min INR	1.8 ± 0.9	1.5 ± 0.6	89909.5	< 0.001
Min lactate	4.7 ± 4.0	2.1 ± 1.58	69894.5	< 0.001
Min platelets	157252 ± 94655.6	177120.8 ± 90595.7	110075.0	< 0.001
Min potassium	3.8 ± 0.8	3.8 ± 0.7	125962.0	< 0.001
Min SBP	75.4 ± 20.3	84.9 ± 19.6	92919.0	< 0.001
Min sodium	137.9 ± 6.1	138.2 ± 5.5	121722.5	0.155
Min WBC	13247.1 ± 8505.4	12.7 ± 6.9	122208.5	0.181
Min DBP	38.7 ± 14.9	44.9 ± 12.7	93559.5	< 0.001
Min SpO_2	81.3 ± 19.0	88.0 ± 12.0	94624.5	< 0.001

Motor response (GCS)	2.9 ± 2.2	4.3 ± 2.0	83488.5	< 0.001
$PaCO_2$	40.0 ± 13.9	39.5 ± 11.6	124352.0	0.321
PaO_2	137.4 ± 102.3	130.9 ± 82.4	121043.0	0.124
pH	7.3 ± 0.1	7.3 ± 0.1	109784.0	< 0.001
Respiratory rate	31.2 ± 15.1	27.5 ± 14.9	107284.5	< 0.001
Temperature	35.2 ± 1.9	36.2 ± 1.4	80674.5	< 0.001
Verbal response (GCS)	1.9 ± 1.5	2.3 ± 1.7	109666.5	< 0.001

BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; GCS: Glasgow coma scale; INR: International normalized ratio; MAP: Medium Arterial Pressure; $PaCO_2$: Partial pressure of carbonic gas in arterial blood; PaO_2: Partial pressure of oxygen in arterial blood; SBP: Systolic blood pressure; SpO_2: Saturation of peripheral oxygen; WBC: White blood cells.



DOI: 10.5492/wjccm.v11.i5.317

Figure 2 Model confusion matrix. As illustrated, the model was able to accurately predict occurrence of death outcome for 63 of 77 patients and non-occurrence for 112 of 131 patients, with true positive and true negative rates of 76.8% and 88.9%, respectively.

79.43%. It is well established in the literature that this type of classifier is generally well suited for high-dimensional problems with highly correlated features (a frequent situation when it comes to medical data)[20]. Our results are consistent with that, as they demonstrate the potential for using random forests to handle clinical and laboratory data from patients under intensive monitoring.

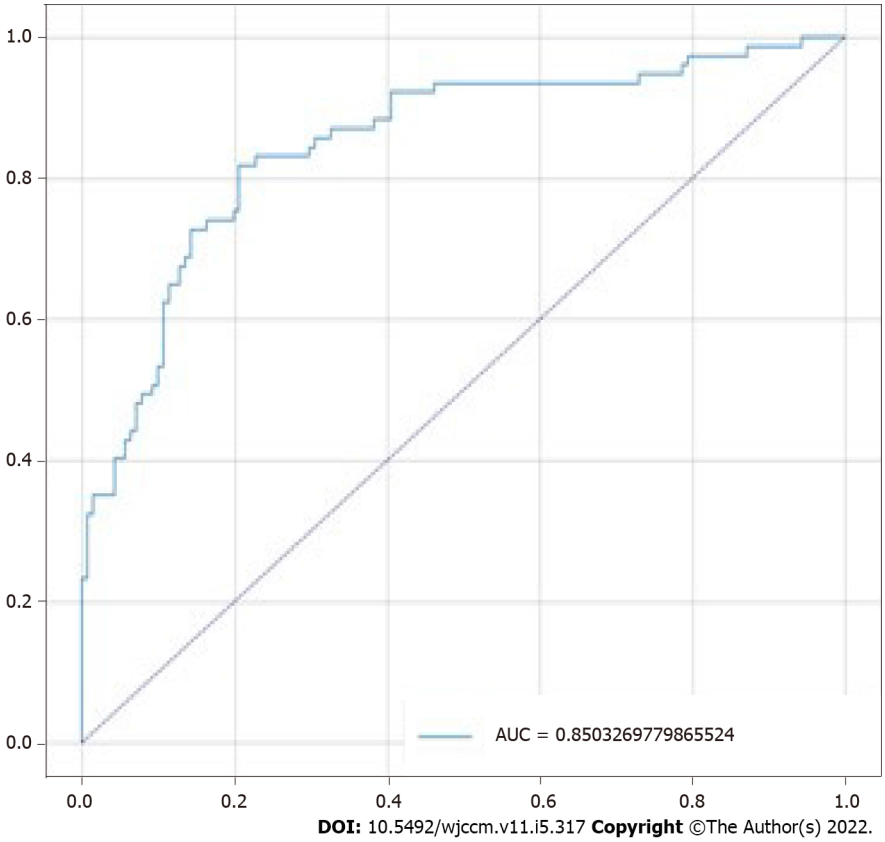
The ICU mortality is high, and the patients require interventions that are cost-effective in order to avoid mortality without inputting unnecessary costs or demand to the medical team. Mortality prediction models work with the objective to assess the severity of the patients so that, based on its findings, the treatment needed can be directed. The analysis presented in this study works in the same way; if we identify those patients that have major mortality rates, faster and better care can be provided in order to prevent the worse outcome[21]. For this purpose, a variety of assessment scores already exist, like APACHE, SAPS or Mortality Probability Model (MPM). The ROC value of our model (0.85) was comparable with some of these highly used models, like 0.836 for APACHE II, or 0.826 for SAPS II[22], which showcase the good results obtained.

Table 2 Percentual importance of variables in the outcome prediction

Variable	Predictive importance, %
Maximum lactate	9.05
Minimum lactate	6.49
Temperature	6.47
Motor GCS	5.25
Maximum BUN	4.35
Minimum WBC	3.31
Minimum creatinine	3.22
Maximum INR	3.15
Minimum HCO_3	2.84
Maximum glucose	2.69
Minimum SpO_2	2.45
pH	2.18
Age	2.09
Minimum INR	1.95
Platelets	1.9
Maximum HCO_3	1.83
Minimum SBP	1.82
Minimum DBP	1.82
Maximum creatinine	1.79
Minimum albumin	1.67
Minimum sodium	1.66
Predominant systemic involvement	1.64
Maximum bilirubin	1.63
Maximum WBC	1.63
PaO_2	1.62
Minimum hemoglobin	1.6
Maximum SBP	1.6
Maximum albumin	1.5
MAP	1.5
Eyes opening GCS	1.46
Respiratory rate	1.41
Minimum calcium	1.4
Maximum hemoglobin	1.39
Minimum platelets	1.35
Minimum BUN	1.28
Hematocrit	1.22
Minimum bilirubin	1.2
$PaCO_2$	1.19
Maximum sodium	1.13
Maximum DBP	1.12
Maximum calcium	0.93

Minimum glucose	0.92
Minimum potassium	0.92
Maximum potassium	0.82
Heart rate	0.72
Verbal GCS	0.42
Intubated	0.15
Disease score	0.14
Maximum SpO_2	0.13

BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; GCS: Glasgow coma scale; INR: International normalized ratio; MAP: Medium Arterial Pressure; $PaCO_2$: Partial pressure of carbonic gas in arterial blood; PaO_2: Partial pressure of oxygen in arterial blood; SBP: Systolic blood pressure; SpO_2: Saturation of peripheral oxygen; WBC: White blood cells.



DOI: 10.5492/wjccm.v11.i5.317

Figure 3 Model receiver operating characteristic curve. The graph demonstrates the relationship between true and false positive rates, which led to an area under the curve of 85%. AUC: Area under the curve.

Furthermore, the machine learning approach to predict mortality in ICU patients has been documented. For example, Veith and Steele[23] developed a LazyKStar model to predict mortality in ICU patients at the time of hospital admission, obtaining a 10-fold validation AUC value of 0.75.A recurrent neural network inputted with 44 clinical and laboratory features from the first 24 h of ICU patient admission proposed by Thorsen-Meyer *et al*[24] achieved an AUC of 0.82. The extreme gradient boosted trees classifier developed by Chia *et al*[25] reached an AUC of 0.83 using 42 predictive variables. The formats and results of these last two studies are comparable to ours, since we reached an AUC of 0.85 using a random forest fed by 50 features.

Due to the COVID-19 pandemic, there was a great growth of publications focused on machine learning models for predicting ICU mortality in a disease-specific manner, such as those by Pan *et al* [16], Lichtner *et al*[26], and Subudhi *et al*[27]. Meanwhile, many of the previous studies in this field also focus on predicting ICU outcomes for specific diseases or morbid conditions, like sepsis or death from pulmonary tuberculosis[11,13,28], which lead to an assessment of parameters specific for the disease studied, somewhat restricting the research. Many of the renowned models and scales for ICU mortality

prediction demand a series of measurements to make their use possible, but not always all the data required are available. In this sense, it is important to understand what the main variables involved related to the outcome of interest (and its prediction) are, so that they can be closely monitored. In our study, lactate level proved to be the most influential one, which is in accordance with its physiological role that indicates poor oxygenation, anaerobic metabolism, acidosis and muscle fatigue, involved in a systemic response of the organ is mand corroborates the findings by Bou Chebl *et al*[29], Villar *et al*[30] and Vincent *et al*[2]. Despite its predictive importance found in our study (15.54%), lactate is not a variable of most scores used, and is not included in APACHE, SAPS or MPM.

Temperature, which is part of APACHE and SAPS, was the second variable that influenced the most the outcome prediction; its variation (hyper or hypothermia) is related with a loss of control of body homeostasis, and the mean valor for death outcome was 35.2 ± 1.9. While we have an increase of nearly 1 point in the mean value for the survival outcome, these data could represent that an increase of the temperature or even fever could be a positive body response, indicating an immune system attempt to fight the pathology[31,32].

The third variable of major impact is the motor GCS punctuation, which is part of GCS, a widely known scale for neurologic damage used in hospital admissions as well as assessment models[33].This motor element has a specific field only in APACHE IV. Lower punctuations in GCS are related with greater neurologic damage, with 3 and 1 as its bottom punctuation for the global and motor scale respectively, the mean of 2.9 ± 2.2 for the death outcome in contrast with the value of 4.3 ± 2.0 for the survival mean demonstrate a considerable difference between those patients since the greatest value possible for the motor component is 6. The stratification of the data based on its predictive value is a great contribution since the variables above discussed account for approximately 27% of the result, while the other 45 for the remaining 73%, indicating that continuous monitoring of them may be of great value. Considering their importance, a detailed survey with either a dataset with per hour measurement of parameters or the data separated by ICU type could lead to more specific approaches for the medical staff.

Despite the good results found, this study faces as its main limitation the incompleteness of the original dataset for many instances regarding important clinical and laboratory variables, which lead to the use of a relatively small quantity of instances to train the predictive model. Since machine learning algorithms are essentially data-driven, a larger amount of data could lead to greater accuracy and a wider generalizability of the model, thus being useful for additional testing and refinement. Another potential limitation is related to the clinically broad nature of the variables analyzed, since the purpose was to study the possible parameters available in the ICU, which contrasts with research focused on the outcomes for a specific disease and, therefore, fed with more specific variables with regards to the considered pathophysiological process.

Although the use of a wide range of clinical and laboratory parameters was critical for our purpose of assessing the predictive significance of the variables in the context of building a model that is not only explainable but also clinically interpretable, this factor may restrict the possibilities of potential datasets to be used to ascertain the reproducibility of the findings, since some parameters may be unavailable. However, since these are variables commonly evaluated in critically ill patients in the ICU, for whom the prognostic evaluation of mortality is more important (in view of their higher mortality rates), we believe that this should not be a limiting factor to the clinical applicability of the proposed model.

CONCLUSION

In the study, it was possible to develop a reliable model for predicting mortality in the ICU, in which the influence of lactate level stands out as the main variable involved in the outcome prediction, followed by temperature and motor GCS. What can be perceived through the research is that machine learning comes to contribute and to make medical practice more efficient, as it allows faster analysis that otherwise would be complex and time-consuming. More than that, it also allows us to critically question existing parameters and methodologies through the results it provides in order to allow improvements that reduce the mortality of patients and are time and cost-effective. This study also highlights the importance of complete and organized registers of ICU patient data in order to enable the development of predictive models towards prevention and prediction of in-hospital bad outcomes.

ARTICLE HIGHLIGHTS

Research background

The monitoring of clinical and laboratory parameters of patients in the intensive care unit (ICU) is an extremely important part of the routine of intensive care staff. Additionally, several scores already utilize these parameters to guide the assistance of these patients. In the meantime, the advance of technological resources, such as the machine learning approach, allows the development of predictive

models capable of being applied to medical practice.

Research motivation

Mortality in the ICU is something that worries and drives the search for alternatives that can help the team in directing treatment to avoid this negative outcome. Therefore, a predictive model that uses the patient's parameters can precisely influence this treatment guidance, improving the cost-effectiveness quickly and safely.

Research objectives

The objective of our study is the development of a binary classifier predictive model between the outcomes of death and non-death in ICU patients. This paper demonstrates the potency of emerging technological realities within the medical field and how it is possible to harness them to improve healthcare practices.

Research methods

Initially, we obtained a set of 1087 instances and 50 variables related to patients admitted to an ICU by using a public database. We calculated frequency and risk rate for categorical variables and means, standard deviations, and the Mann-Whitney *U* test for numerical variables. Afterwards, we divided the data for the application in training of the predictive model based on the Random Forest algorithm and then to test the effectiveness of the model.

Research results

Among the 50 variables associated with death outcome, the maximum and minimum lactate values were the most important predictors (15.54%) followed by temperature (6.47%), and motor Glasgow coma scale punctuation (5.25%). The Random Forest binary classifier predictive model (death and no death) showed accuracy of 80.28%, sensitivity of 81.82%, specificity of 79.43%, positive predictive value of 73.26%, negative predictive value of 84.85%, F1 score of 0.74, and area under the curve score of 0.85.

Research conclusions

This study demonstrated the development of a predictive model with high accuracy, sensitivity, and specificity for ICU patients by applying a machine learning approach, the Random Forest algorithm, to clinical and laboratory data.

Research perspectives

The proper registration of patient parameters, as well as the availability of more and larger databases and even further development of digital tools, can enhance machine learning approaches, enabling the refinement of predictive models and patient care.

FOOTNOTES

Author contributions: Caires Silveira E collected and entered the data, performed the data analysis/statistics and interpretation, and participated in preparation and review of manuscript; Mattos Pretti S and Santos BA participated in the preparation of manuscript and wrote the literature analysis/search; Santos Corrêa CF and Madureira Silva L participated in review of manuscript; Freire de Melo F designed the research and participated in review of manuscript.

Institutional review board statement: For this study, there was no need for an appraisal by an ethics committee, since only publicly available anonymized data were used.

Informed consent statement: This manuscript does not involve "Signed Informed Consent Form", as it was produced from previously anonymized, publicly available and free of charge data, obeying the norms of medical bioethics. Thus, there was no direct or even indirect contact between researchers and patients, with no necessity for "Signed Informed Consent Form" to carry out our study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

Country/Territory of origin: Brazil

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S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Wang JJ

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World Journal of Critical Care Medicine

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World J Crit Care Med 2022 September 9; 11(5): 330-334

DOI: 10.5492/wjccm.v11.i5.330

ISSN 2220-3141 (online)

CASE REPORT

Acute kidney injury associated with consumption of starfruit juice: A case report

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Specialty type: Toxicology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chen BH, Taiwan; Tu GW, China

Received: January 6, 2022
Peer-review started: January 6, 2022
First decision: March 24, 2022
Revised: May 6, 2022
Accepted: July 18, 2022
Article in press: July 18, 2022
Published online: September 9, 2022

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Abstract

BACKGROUND

This study aims to highlight the potential serious complications of acute kidney injury (AKI) resulting from the consumption of excessive amounts of starfruit, a common traditional remedy.

CASE SUMMARY

A 78-year-old male with a past medical history of hypertension, diabetes mellitus and hyperlipidemia without prior nephropathy presented to the emergency department (ED) with hiccups, nausea, vomiting and generalized weakness. In the preceding 1 wk, he had consumed 3 bottles of concentrated juice self-prepared from 1 kg of small sour starfruits. His serum creatinine was noted to be 1101 μmol/L from baseline normal prior to his ED visit. He was diagnosed with AKI secondary to excessive starfruit consumption.

CONCLUSION

Consumption of starfruit can cause acute renal failure, with a good outcome when promptly identified and treated.

Key Words: Acute kidney injury; Acute renal failure; Starfruit; Hemodialysis; Case report

Core Tip: Physicians should have a high index of suspicion on possible interactions and toxicities that may occur with the use of traditional medications in combination with prescription drugs in susceptible patients. This report highlights the toxicity of starfruit when consumed as a traditional remedy for diabetes mellitus resulting in acute kidney injury.

Citation: Zuhary TM, Ponampalam R. Acute kidney injury associated with consumption of starfruit juice: A case report. *World J Crit Care Med* 2022; 11(5): 330-334
URL: https://www.wjgnet.com/2220-3141/full/v11/i5/330.htm
DOI: https://dx.doi.org/10.5492/wjccm.v11.i5.330

INTRODUCTION

The starfruit (Averrhoa carambola) is a popular fruit in tropical countries due to its nutritional and medicinal benefits[1], and is used to treat various ailments such as diabetes mellitus, rheumatism, and cough. The starfruit is used as a traditional remedy in Asian countries such as Malaysia and Indonesia to treat diabetes mellitus due to its hypoglycemic properties[2]. Despite its frequent consumption, many people are unaware of the dangers of overindulging in starfruit. When consumed in large quantities, the fruit contains high levels of oxalic acid, which can be nephrotoxic. Starfruit-induced neurotoxicity and nephrotoxicity, which manifests as acute kidney injury (AKI) in individuals with underlying renal dysfunction, is well documented[3,4]. AKI in individuals with normal renal function is rare. We present a case report of AKI following the consumption of starfruit.

CASE PRESENTATION

Chief complaints

A 78-year-old male presented to the emergency department (ED) with hiccups, nausea, vomiting and generalized weakness.

History of present illness

In the preceding week, he had consumed 3 bottles of concentrated juice which were self-prepared from 1 kg of starfruits. Following ingestion of the third bottle of the fruit juice, he developed bouts of severe nausea and vomiting without abdominal pain or diarrhea.

History of past illness

He had a past medical history of hypertension, diabetes mellitus and hyperlipidemia.

Personal and family history

No significant family history.

Physical examination

On arrival at the ED, his vital signs were stable (temperature was 36.8°C, pulse rate 60 bpm, respiratory rate 18 breaths/min, and blood pressure 161/78 mmHg) and there was no pitting edema. Examinations of his cardiovascular, respiratory, abdominal and neurological systems were normal.

Laboratory examinations

Laboratory examination results are shown in Figure 1 and Table 1.

Imaging examinations

No imaging was undertaken.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient was initially seen in the ED and admitted under renal medicine for specialized care.

FINAL DIAGNOSIS

Acute kidney injury.

Table 1 Trend in patient's blood investigations

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 13	Day 17	Day 24	Day 60	Day 135
Renal function											
Serum creatinine (μmol/L)	1101		680	659	495	340	328	208	177	127	99
Serum urea (mmol/L)	38.1		23.1	27.1	22.0	14.5	25.2	17.4	10.6	12.4	6.2
Electrolytes											
Sodium (mmol/L)	134		142	146	147	137	135	136	138	140	144
Potassium (mmol/L)	4.4		3.5	3.5	3.1	4.0	4.3	4.0	4.1	3.8	3.9
Chloride (mmol/L)	101		105	102	100	98	101	102	105	108	110
Bicarbonate (mmol/L)	15.9		22.8	26.8	31.1	24.6	28.3	23.7	24.6	23.5	24.9
Magnesium (mmol/L)	0.91										
Liver function											
Total protein (g/L)	60										76
Serum albumin (g/L)	32										41
Total bilirubin (mmol/L)	07										09
Alkaline phosphatase (U/L)	58										65
Alkaline transaminase (U/L)	57										17
Routine tests											
White blood cells (× 10^9/L)	9.33					10.25					9.89
Neutrophil (%)	78.8					74.6					74.1
Lymphocytes (%)	11.1					11.6					15.9
Hemoglobin (g/dL)	12.3					13.8					14.1
Platelet count (× 10^9/L)	208					307					281
Coagulation											
APTT (secs)	27.0					28.5					
Prothrombin time (secs)	11.2					11.4					
Other indicators											
Creatine kinase (U/L)	7224			4755	2863	754		84			84
PTH (pg/mL)	11.0										
Urine creatinine (μmol/L)			5233					3862	7747		8035

APTT: Activated partial thromboplastin time; PTH: Parathyroid hormone.

TREATMENT

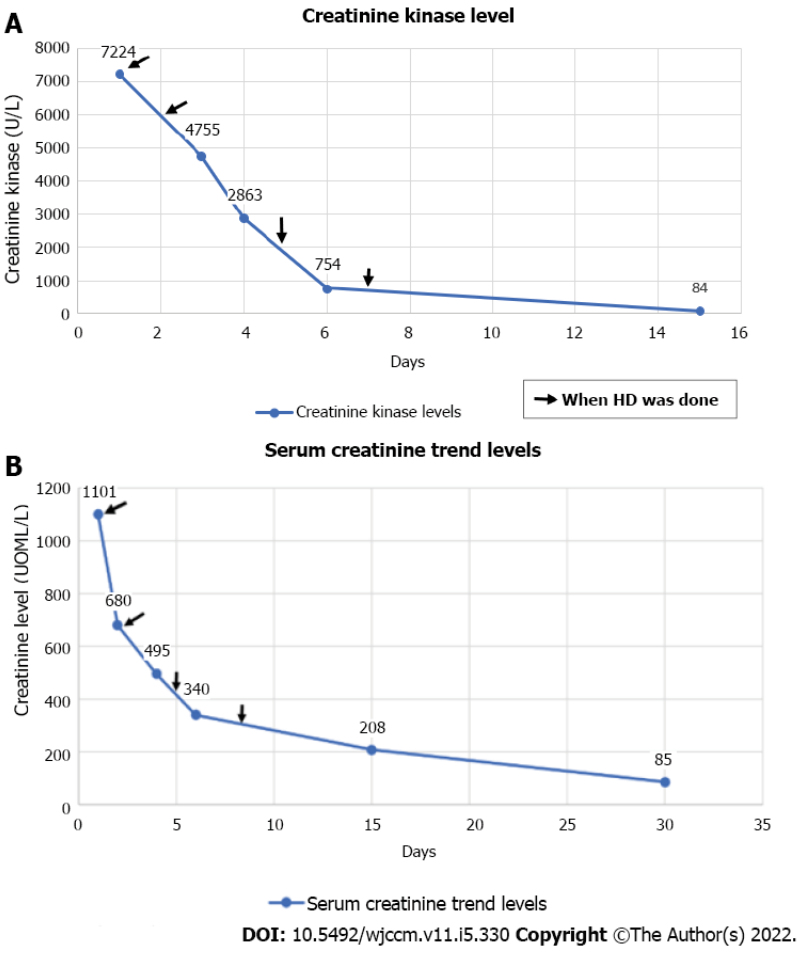
The patient was treated with 4 sessions of hemodialysis and supportive care such as intravenous fluid. After each session of hemodialysis, blood tests to determine renal function were repeated. Progressive improvement in renal function was noted with each session of hemodialysis.

OUTCOME AND FOLLOW-UP

The patient's renal function returned to normal.

DISCUSSION

Starfruit has several toxins including caromboxin, an excitatory central nervous system stimulant and



DOI: 10.5492/wjccm.v11.i5.330

Figure 1 Laboratory examination results. A: Trend in creatinine kinase following hemodialysis; B: Trend in serum creatinine.

oxalate a nephrotoxic agent[5-7]. The sour type of starfruit has higher levels of oxalate than the sweet type. Homemade and medicinal supplements often have high levels of oxalate. When consumed in large amounts, especially when fasting or dehydrated, deposits of calcium oxalate crystals in the renal tubules lead to kidney damage[6]. Chronic kidney disease has been identified as a major risk factor for starfruit-induced kidney toxicity. Starfruit juice volume of approximately 25 mL is known to cause nephrotoxicity in patients with chronic kidney disease. Other known risk factors include dehydration, the amount of starfruit ingested, and consumption on an empty stomach. Patients with starfruit toxicity show gastrointestinal symptoms such as nausea, vomiting, and abdominal discomfort immediately after ingestion. These symptoms are believed to be due to the direct corrosive effects of dietary oxalates rather than systemic effects[8]. This may be followed by a decrease in urinary output, which can lead to renal dysfunction and acute renal failure. Typical histological findings are the intraluminal and intraepithelial deposition of colorless oxalate crystals. There is no specific treatment for acute kidney damage from starfruit. In patients requiring renal replacement therapy, hemodialysis and hemoperfusion are preferred[9].

Our patient had no evidence of pre-existing renal failure or other contributory factors predisposing to AKI such as sepsis, dehydration, nephrotoxic drugs or obstructive urological causes based on clinical evaluation and tests done. In addition, over the course of four sessions of hemodialysis, he had gradual restoration of his renal function. The temporal relationship between the ingestion of large amount of fruit juice and the onset of symptoms in this case strongly suggests starfruit intoxication as the transient and reversible etiology likely due to resolving oxalate nephropathy.

CONCLUSION

In Asian countries where starfruit is commonly consumed as a traditional remedy, it is imperative for emergency physicians to be aware of starfruit toxicity in patients with unexplained AKI. This will help identify and treat these patients promptly to prevent starfruit-induced nephrotoxicity. Patient history is the key to reaching an early diagnosis. It is essential to prevent starfruit nephrotoxicity by educating the public and especially diabetics on the risks of consuming excess starfruit. Consumption of starfruit as a

traditional remedy to control blood sugar levels in diabetics should be discouraged by educating the public.

ACKNOWLEDGEMENTS

We thank the staff of both the Emergency Department and Nephrology Departments for their major contributions in the daily care of this patient.

FOOTNOTES

Author contributions: Zuhary TM and Ponampalam R equally contributed to this case study.

Informed consent statement: Informed written consent was obtained from the patient.

Conflict-of-interest statement: All authors report no relevant conflict of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Singapore

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S-Editor: Wu YXJ
L-Editor: Webster JR
P-Editor: Wu YXJ

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World Journal of Critical Care Medicine

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World J Crit Care Med 2022 September 9; 11(5): 335-341

DOI: 10.5492/wjccm.v11.i5.335

ISSN 2220-3141 (online)

CASE REPORT

Cardiac arrest due to massive aspiration from a broncho-esophageal fistula: A case report

Gustavo Lagrotta, Mina Ayad, Ifrah Butt, Mauricio Danckers

Specialty type: Critical care medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Kumar N, India; Liu YC, China; Xu L, China

Received: January 20, 2022
Peer-review started: January 20, 2022
First decision: April 13, 2022
Revised: May 29, 2022
Accepted: July 31, 2022
Article in press: July 31, 2022
Published online: September 9, 2022

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Abstract

BACKGROUND

Tracheo and broncho esophageal fistulas and their potential complications in adults are seldom encountered in clinical practice but carries a significant morbidity and mortality.

CASE SUMMARY

We present a case of a 39-year-old otherwise healthy man who presented to our hospital after ingestion of drain cleaner substance during a suicidal attempt. He unexpectedly suffered from cardiac arrest during his stay in the intensive care unit. The patient had developed extensive segmental trachea-broncho-esophageal fistulous tracks that led to a sudden and significant aspiration event of gastric and duodenal contents with subsequent cardiopulmonary arrest. Endoscopic evaluation of extension of fistulous track proved a slow and delayed progression of disease despite initial management with esophageal stenting for his caustic injury.

CONCLUSION

The aim of this case presentation is to share with the reader the dire natural history of trachea-broncho-esophageal fistulas and its delayed progression. We aim to illustrate pitfalls in the endoscopic examination and provide further aware-ness on critical care monitoring and management strategies to reduce its morbidity and mortality.

Key Words: Tracheoesophageal fistula; Broncho esophageal fistula; Caustic ingestion; Cardiopulmonary arrest; Critical care; Case report

Core Tip: Trachea-esophageal and broncho-esophageal in the setting of caustic ingestion is an unusual complication associated with high morbidity and mortality. Close monitoring of the gastrointestinal tract patency and motility is critical to avoid gastric distention and large aspiration events with detrimental consequences. Although there is no general consensus on the initial approach to patients with fistula formation, our case proposes serial esophagogastroduodenoscopy and flexible bronchoscopy for at least 6 mo as well as a low threshold for surgical referral when progression of disease or new findings are encountered.

Citation: Lagrotta G, Ayad M, Butt I, Danckers M. Cardiac arrest due to massive aspiration from a broncho-esophageal fistula: A case report. *World J Crit Care Med* 2022; 11(5): 335-341
URL: https://www.wjgnet.com/2220-3141/full/v11/i5/335.htm
DOI: https://dx.doi.org/10.5492/wjccm.v11.i5.335

INTRODUCTION

Injuries from caustic substance ingestion are associated with varying grades of damage to the gastrointestinal and respiratory tract including esophagitis, mucosal burns, necrosis and perforation, stenosis, and rarely, trachea-esophageal (TEF), and broncho-esophageal (BEF) fistulas. Suicidal caustic ingestion strongly correlates with severity of injury and carries high morbidity and mortality[1]. We present the case of a young man after suicidal caustic ingestion of drain cleaner fluid who developed a sudden massive gastric and duodenal content aspiration into his airway through acquired large TEF and BEF fistulas leading to cardiopulmonary arrest.

CASE PRESENTATION

Chief complaints

A 39-year-old man arrived at our emergency department from another institution where he had been endotracheally intubated for airway protection.

History of present illness

The patient had sought medical attention five hours after a suicidal attempt where he ingested an unknown amount of drain cleaner liquid that contained sodium hydroxide, potassium hydroxide, and carbonyl diamide.

History of past illness

The patient had a free previous medical history.

Physical examination

Upon arrival to our facility, his vital signs were stable. His physical exam revealed edematous oral mucosa and chemical injuries to the face.

Laboratory examinations

His initial laboratory data was remarkable for a white blood cell count of 12.9 × 10^3/μL and a D-dimer > 5250 ng/mL DDU.

Imaging examinations

Chest computer tomography (CT) with contrast revealed thickening and submucosal edema of the esophageal and gastric wall, along with trace para-esophageal and peri-gastric stranding and fluid. No free air was reported.

FINAL DIAGNOSIS

Tracheo and broncho esophageal fistulas leading to massive aspiration and cardiac arrest.

TREATMENT

He was started on a proton pump inhibitor, intravenous fluids, and prophylactic antibiotics. A tracheostomy and jejunostomy tube were placed on hospital day 13. He was noted to have bouts of coughing during routine sedation-awakening trials and with reduction in sedatives. On hospital day 18, he became acutely hypoxic, and his oxygen saturation decreased to 50% followed by pulseless electrical arrest. Advanced cardiopulmonary resuscitation was initiated with recovery of spontaneous circulation after two 5-min rounds of cardiopulmonary resuscitation. Copious amounts of frothy, yellow-tinted secretions were noted from the tracheostomy in-line suction setup. No oral secretions were noted during oral cavity suction. A nasogastric tube was placed for gastric cavity decompression and approximately 400-500 mL of fluid were suctioned. Figure 1 demonstrates chest imaging obtained prior and post cardiopulmonary arrest highlighting the patient's acute clinical change. On day 22, the patient underwent successful placement of a 1.8 cm in outer diameter and 12.3 cm in length fully covered esophageal stent.

The patient's hospital course was complicated by acute respiratory distress syndrome and recurrent septic shock secondary to aspiration pneumonia. He was eventually liberated from mechanical ventilation and transitioned to a tracheostomy collar. He continued on enteral nutrition through a jejunostomy feeding tube. He left the intensive care unit on day 40 and was discharged home with home-health on day 114.

OUTCOME AND FOLLOW-UP

His endoscopy surveillance revealed progression and further extend of disease. Bronchoscopies performed on day 1 and day 8 as noted in Figure 2 demonstrate the progression of the insult. Bronchoscopy performed after 17 wk revealed new tracheoesophageal fistula with esophageal lumen opening at midway through posterior wall of the trachea (Figure 3A and B). His prior bronchoscopy at 7 wk had shown protrusion of esophageal stent through the left main broncho-esophageal fistula without any additional fistulous tracts (Figure 3C). Esophagoduodenoscopy (EGD) performed 7 mo after initial presentation visualized tracheostomy tube through a combined lumen formed by the esophagus and trachea (Figure 3D). Distal to the tracheostomy tube, a double lumen is identified with the esophagus opening at the proximal end of the stent (Figure 3E) as well as a complete obliteration of the stent in his distal end due to in-growth tissues (Figure 3F). The patient has been referred for cardiothoracic surgical evaluation where he will complete nutritional optimization prior to potential surgical intervention. Chron-ology of events is listed in Table 1.

DISCUSSION

Caustic ingestion remains a rare but potentially catastrophic mechanism for injury leading to significant morbidity and mortality. Specific management guidelines have yet to be defined[2]. Injury severity is determined by multiple factors including type of agent, its concentration, amount consumed, and time of contact with gastrointestinal mucosa. Agents can be either acidic or alkali. Our patient ingested drain cleaner liquid, predominantly an alkali substance.

TEF is a delayed and unusual complication that occurs approximately in 3% of patients with caustic ingestion[2]. BEF are not extensively described in the literature and their true incidence unknown. The rarity of BEFs is likely due to the anatomical relationship between the left mainstem bronchus and the esophagus. The thoracic esophagus extends caudally towards the diaphragmatic hiatus, passing posteriorly to the trachea, the tracheal bifurcation, and the left main stem bronchus[3]. The area of contact of the posterior wall of the left main bronchus with the anterior wall of the esophagus, in contrast to that of the trachea, is significantly smaller, making left main BEFs less likely to develop than TEF.

Hemorrhage, thrombosis, and inflammation with edema occur within the first 24 h. If caustic ingestion is severe enough, transmural necrosis leads to perforation and regional fistulous tract formation. TEFs and BEFs can lead to sepsis, aspiration pneumonia, acute respiratory distress syndrome, strictures, malignancy among other systemic complications[2]. In our patient, the fistulous tract was significant enough to allow for large amounts of gastric and duodenal content to reach the airway causing hypoxemia and cardiopulmonary arrest.

Medical literature on the incidence of cardiopulmonary arrest due to aspiration through a BEF is lacking, and its incidence is not defined. We infer that our patient's aspiration leading to his arrest was

Table 1 Timeline of major events in chronological order

Event	Time
Admission to hospital/ICU	Day 0
EGD #1	Day 0
Bronchoscopy #1	Day 1
Bronchoscopy #2	Day 8
Cardiac arrest	Day 18
Esophageal stent placement with EGD #2	Day 22
Bronchoscopy #3	7 wk
Hospital discharge	16 wk
Bronchoscopy #4	17 wk
EGD #3	28 wk

ICU: Intensive care unit; EGD: Esophagoduodenoscopy.

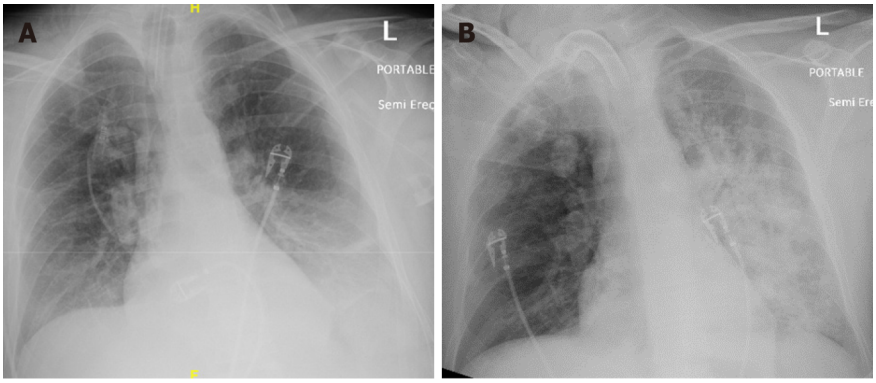

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Figure 1 Chest X-ray. A: Chest X-ray on the left was obtained one day prior to cardiac arrest which shows bibasilar atelectasis; B: Chest X-ray on the right obtained following episode of cardiopulmonary arrest showing significant patchy airspace opacities occupying most of left hemithorax.

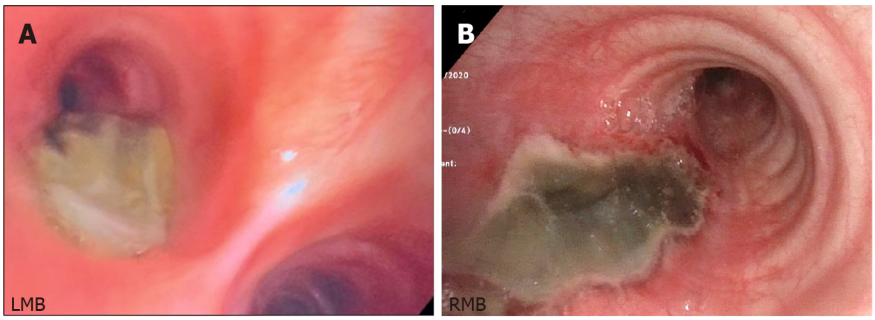

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Figure 2 Flexible bronchoscopy. A: Day 1: Two-centimeter bronchoesophageal fistula (asterisk) with adjacent yellow tinged devitalized mucosa on the posterior wall of left main bronchi; B: Day 8: Further delineation of fistulous track (asterisk) with necrotic mucosa and well-defined borders. LMB: Left main bronchi; RMB: Right main bronchi.

due to increased output through a persistently large fistulous track in the setting of transient duodenal outlet stenosis from mucosal damage and impaired gastrointestinal motility. Our patient exhibited large amounts of bile-colored tracheal secretions in the peri-arrest period confirming a high output fistulous passage of duodenal content. Although in our case the volume we aspirated through naso-gastric suctioning was 400-500 mL, the exact volume of gastric content aspirated is unknown. However, it was large enough to infiltrate the lingula and left lower lobe.

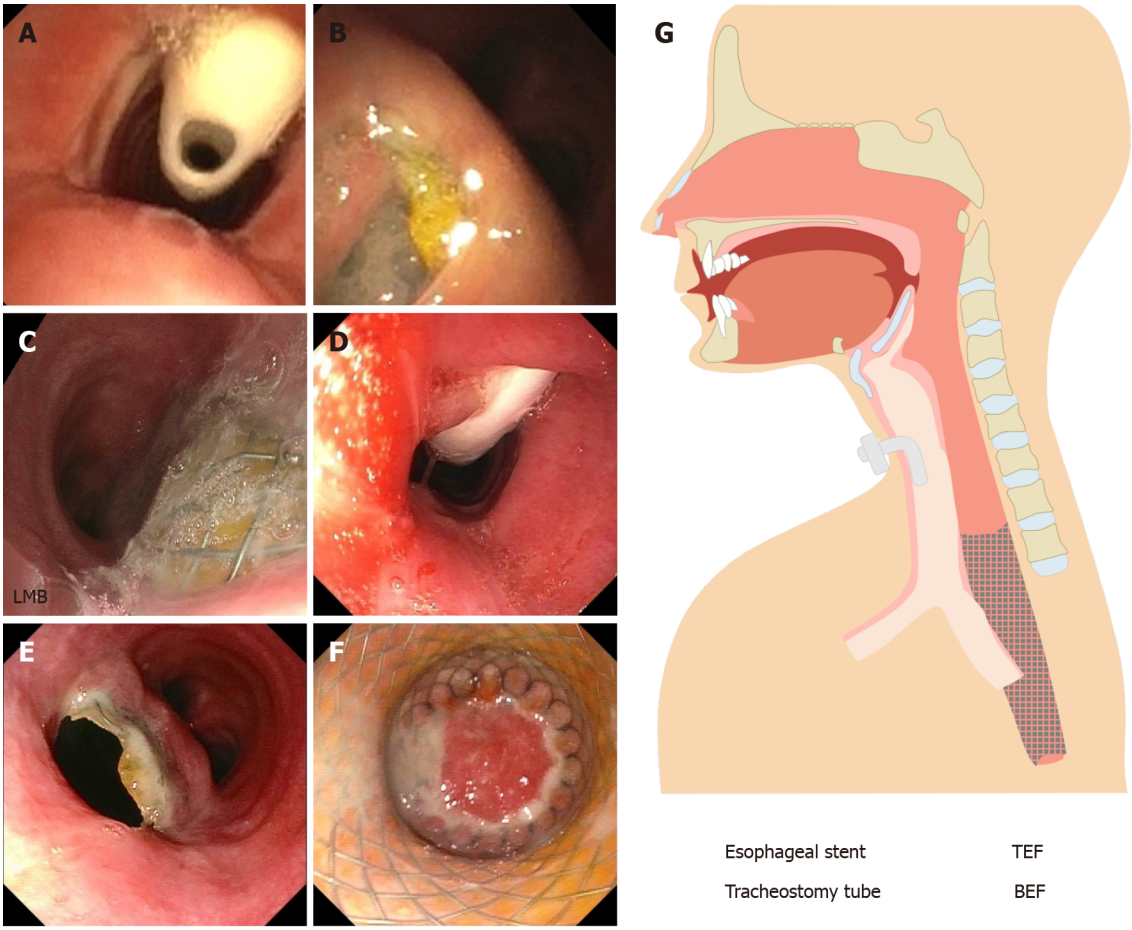

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Figure 3 Flexible bronchoscopy at 17 wk. A: Visualization of tracheostomy tube (asterisk) shortly after bronchoscope is advanced through vocal cords; B: Esophageal lumen visualized at the level of mid-trachea confirming TEF. Flexible Bronchoscopy at 7 wk; C: Protruding esophageal stent through left main bronchi BEF. Esophagoduodenoscopy at 28 wk; D: Visualization of tracheostomy tube (asterisk) through a combined lumen of the esophagus and trachea at 14 cm; E: Proximal end of the esophageal stent located below the end of the tracheotomy at 23cm with a double lumen track, esophagus at 8 o'clock and trachea at 2 o'clock; F: Complete obliteration of esophageal stent due to in-growth of tissue at 35 cm (asterisk); G: Schematic diagram. LMB: Left main bronchi; TEF: Tracheoesophageal fistula; BEF: Bronchoesophageal fistula.

The incidence of aspiration pneumonia related to corrosive ingestion has been estimated in up to 4.2% of cases with a mortality up to 60%[4]. Due to high risk of aspiration, enteral nutrition is often restricted[4]. In addition, caloric restriction and malnutrition further lead to recurrent pulmonary infections, bronchopneumonia, and sepsis[5]. Alternative means of enteral nutrition through the insertion of a jejunostomy tube were sought in our patient to enhance nutritional state as well as to promote fistula healing. A high index of suspicion should be maintained for functional or anatomic gastrointestinal tract obstruction as a consequence of caustic injury and should be considered when addressing nutritional support to select the most suitable nutritional route.

Risk stratification is needed during the initial approach. Symptoms such as dysphagia, hematemesis, stridor, cough, respiratory distress, drooling, and abdominal pain have been described. A sudden bout of uncontrolled paroxysmal cough, a reported symptom associated with BEF[6], was witnessed in our patient while mechanically ventilated during daily sedation awakening trials suggesting aspiration events and persistent fistula.

There is no consensus within the medical community of the initial and emergent management of TEF/BEF after caustic ingestion. In 2015, the World Society of Emergency Surgery recommended a management algorithm which includes both endoscopy and CT imaging as part of the initial assessment [7]. Our patient underwent both, esophagogastroduodenoscopy and non-contrast CT scan within the first twenty-four hours of ingestion. Figure 4 demonstrates initial esophagoduodenoscopy findings. In order to quantify the severity of the injury, we utilized the Zargar classification system which placed him in the IIIB category[8]. This grading is useful for predicting systemic complications, respiratory failure, nutritional autonomy, and survival. In general, the degree of esophageal injury at endoscopy is a predictor of systemic complication and death with a 9-fold increase in morbidity and mortality for every increased injury grade[9] which aligns with our case study. An important tool for the clinician about risk rather than timing.

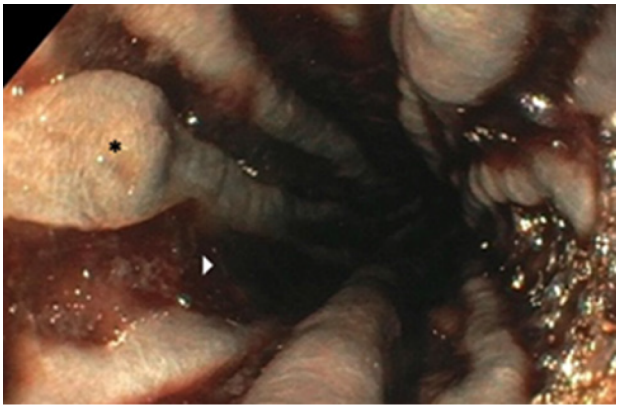

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Figure 4 Esophagoduodenoscopy. Extensive esophageal esophagitis with devitalized mucosa (asterisk) and deep brownish black ulcers (arrowhead).

However, risk stratification cannot accurately predict the depth of necrosis which could lead to inappropriate non-operative management and/or unnecessary surgical resection[2]. In order to properly evaluate the extent of necrosis, we propose that there is a benefit for surveillance endoscopic examination through EGD and flexible bronchoscopies for early fistula detection and therapeutic interventions. This would also serve for the monitoring of long term sequelae such as airway stenosis, or such in our case, further development of fistulous tracks. The interval of bronchoscopies would be dictated by endoscopic findings. In our case, evidence of a large newly detected TEF occurred 4 mo after the initial event. Prior biweekly and monthly bronchoscopies only reported the known BEF. It is reasonable to suggest monthly endoscopic surveillance in patients with high Zargar Score for at least 4-6 mo following the initial ingestion. In patients who are able to be discharged from the hospital, surgical referral should be sought if endoscopic examination does not show a favorable course, new fistulous tracks are detected, or if the patient's symptoms severely impair quality of life.

The treatment of TEFs and BEFs is based on previous case reports, reviews, and case series, along with experts' opinions. In our case, a multidisciplinary team agreed on the placement of an 18 mm × 123 mm fully covered esophageal wall stent. According to the World Journal of Emergency Surgery, endoscopic treatment is the gold standard for closing large esophageal defects such suspected in our patient for the exam of injury during initial endoscopic examination. Self-expandable stents have showed to have a higher success rate and lower mortality rate when compared to surgical approach [10]. Our patient underwent self-expandable sent placement due to the clinical complexity and added surgical risk in the setting of a recent cardiac arrest. This case illustrates both the prolonged hospital course of a cardiac arrest survival due to delayed complications of a BEF associated with functional impairment and also the protracted progression of the disease more than 6 mo later.

CONCLUSION

In conclusion, TEF and BEF in the setting of caustic ingestion is an unusual complication associated with high morbidity and mortality. Early and frequent endoscopic evaluation of the upper gastrointestinal tract and bronchial tree, as well as maintaining a high index of clinical suspicion, are necessary for its prompt recognition. This will lead to early detection of delayed complications including new fistulous tracks, and timely institution of therapeutic interventions. We remind the reader of the importance of close monitoring of the gastrointestinal tract patency and motility to avoid gastric distention and large aspiration events with detrimental consequences. Although there is no general consensus on the initial approach to patients with fistula formation, our case proposes serial EGDs and flexible bronchoscopy for at least 6 mo as well as a low threshold for surgical referral when progression of disease or new findings are encountered.

ACKNOWLEDGEMENTS

The authors would like to acknowledgment Dr. Gonzalez H and Dr. Bethencourt-Mirabal A for the revision provided to the manuscript, and Dr. Kaplan S, Dr. Heller D and Dr. Morgan D, for their insight on the esophagoduodenoscopic and bronchoscopic findings.

FOOTNOTES

Author contributions: Danckers M contributed conceptualization, writing original draft preparation and follow up revisions, image acquisition and editing, illustration preparation and data verification; Lagrotta G contributed writing original draft, image review and verified data; Ayad M contributed reviewing, data and image acquisition; Butt I contributed reviewing.

Informed consent statement: Written consent for publication was obtained from the patient health care proxy.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: United States

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S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

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