Predicting ICU Admission in Patients With COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) has become a global pandemic, affecting the lives of many and challenging unprepared healthcare systems. Due to its recency, there is still much that is unknown about the virus. Blood cell counts as a reflection of virus infection and recovery have played a vital role in COVID-19 immune response, however their correlation with symptom severity has yet to be thoroughly explored.

In this study, the blood counts, and various demographic factors of 383 samples were studied. Anonymized patients in this sample had data collected from Hospital Sírio-Libanês, São Paulo, Brazil. This data was analyzed to determine likelihood of intensive care unit (ICU) admission in patients with COVID-19 based on the blood counts of hemoglobin, platelets, linfocitos (lymphocytes), leukocytes, and neutrophils (neutrophils), as well as four relevant covariates: body temperature, age, gender, and immunocompromised status. From the model, it was determined that neutrophil and leukocyte counts had the greatest predictive influence on ICU admission, while age and immunocompromised status had the least.

With the findings of this study, doctors and other medical health professionals can use the counts of various blood factors in parallel with data on basic relevant covariates to predict infection severity in patients with COVID-19.

Keywords

Computational epidemiology; Disease Detection and Diagnosis; Coronavirus disease 2019; Public Health; Machine Learning

Introduction

Coronavirus disease 2019

The rise of Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) virus, has had devastating impacts on existing healthcare systems and infrastructure worldwide. It led to a global shortage of personal protective equipment (PPE), like N95 respirators, face shields, and gloves, as well as a shortage of ICU beds and ventilators [1]

From its first report in December 2019 in Wuhan, China, [2] the virus has infected about 605 million people and led to the deaths of over 6.5 million people worldwide, [3] as of September 6th, 2022. [2,3] There is a wide array of symptoms of COVID-19 including, but not limited to, fever, headache, cough, fatigue, loss of taste, and loss of smell. These symptoms vary depending on the person and approximately one third of infected people do not develop any symptoms In the triage of patients with COVID-19, some of the most critical symptoms to determine infection severity are fever (>38° C) and cough. [4,5]

Intensive Care Unit (ICU) admission

Intensive care is defined as a provision for patients with potentially recoverable conditions who would benefit more from detailed observation and invasive treatment than from treatment that can safely be provided in general wards or high dependency areas. Intensive care is typically reserved for those with potential or established organ failure (most commonly lung failure, but also other organ failures). According to an analysis by Smith, G. and Nielsen, M. (1999), criteria for ICU admission can include: a threatened airway, any form of respiratory arrest, a respiratory rate of more than 40 or less than 8 breaths per minute, an oxygen saturation of less than 90% on greater than or equal to 50% oxygen, cardiac arrest, a pulse rate less than 40 or greater than 140 beats minute, a systolic blood pressure less than 90 mm Hg, a sudden fall in consciousness (fall in Glasgow coma score greater than 2 points), repeated or extended seizures, or an increasing arterial carbon dioxide tension with respiratory acidosis.[6] Basic care in an ICU setting involves monitoring of heart rate, blood pressure, respiratory rate, pulse oximetry, hourly urine output, body temperature, and blood gases.[6] More extreme situations may demand use of advanced techniques including breathing assistance from artificial ventilators, dialysis machines and/or intravenous infusions via tubes and drips. [7]

The requirement of intensive care among patients hospitalized with COVID-19 varies between 5% to 32%, depending on country.[8] The United States largely had the highest number of ICU admissions due to COVID-19 globally from July 2020 to August 2022, the count reaching almost 29,000 patients at one time in January of 2021.[9] Some studies have reported that a variety of factors, including age, gender, and comorbidities, are linked with the severity of COVID-19 disease and ICU admission. [8,10]

Blood cells

Blood cells play a significant role in the human body's immune system. There are three main types of blood cells: red blood cells, platelets, and white blood cells. Red blood cells (RBC), sometimes referred to as red cells, red blood corpuscles, haematids, erythroid cells or erythrocytes, are the most common type of cell found in blood and are responsible for delivering oxygen to tissues throughout the body via the circulatory system. Platelets, or thrombocytes, play a central role in clotting blood to stop or prevent bleeding and support healing of wounds. White blood cells (WBC), or leukocytes, are the most relevant form of blood cell in terms of immunity, illness susceptibility, and recovery rate. Specific varieties of white blood cells include monocytes, granulocytes (neutrophils, eosinophils, and basophils), and lymphocytes (T cells and B cells). WBC help defend the body against bacterial, viral, fungal, and parasitic infections. [11]

In this study, hemoglobin, platelets, lymphocytes, leukocytes, and neutrophils were the selected blood factors of study. Hemoglobin is a metalloprotein in red blood cells of almost all vertebrates as well as the tissues of some invertebrates that carries oxygen throughout the body. Hemoglobin in blood carries oxygen from the respiratory organs to the rest of the body.[12] Platelets, as defined above, help the body form blood clots to reduce bleeding and support wound recovery. Overall leukocyte (WBC) count was also studied (defined above), in addition to the counts of two specific types of WBC – lymphocytes and neutrophils. Lymphocytes can be of two types: T lymphocytes (T cells) and B lymphocytes (B cells). T cells control your body's immune system response and directly attack and kill infected cells, while B cells make antibodies - proteins that target viruses, bacteria, and other foreign bodies. neutrophils also aid in immune system response – monitoring the bloodstream for signs of microbial infection and killing unwanted pathogens when found. [13]

Various empirical studies have investigated links between white blood cell (WBC) count and COVID-19 severity, but a firm conclusion has yet to be reached. Some studies present that those with higher WBC count display heightened severity of COVID-19, while others found that a lower WBC increased likelihood of severe illness and death.[14,15] A firm conclusion has yet to be reached, and a broader analysis of the effects of various blood counts (rather than just WBC) on COVID-19 severity has yet to be robustly researched. This study examined the relationship between the count of various blood factors - hemoglobin, leukocytes, lymphocytes, neutrophils, and platelets - to body temperature in patients with COVID-19 to gain insight into the various factors in blood that contribute to COVID-19 severity.

General

In this study, a statistical model was created to predict ICU admission using the counts of the studied blood factors: hemoglobin, leukocytes, lymphocytes, neutrophils, platelets and various clinical covariates: body temperature, age (above 65 years), gender, and immunocompromised status, defined as the state of having a weakened immune system which may be caused by certain diseases or other conditions like cancer, diabetes, etc.[16] This model was used to parse the importance of blood cell counts and clinical covariates on predicting ICU admission. Understanding these importances would be vital to improving healthcare efficiency, as doctors and other medical health professionals can predict and prepare what materials may be necessary to care for patients, such as ICU beds or ventilator systems.

Methods

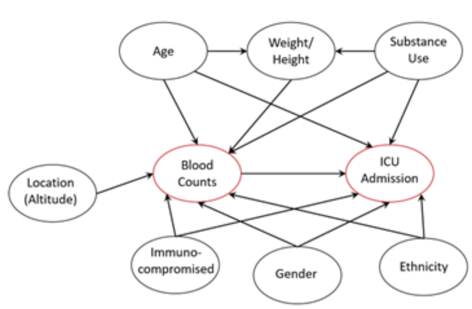
A dataset, *COVID-19 - Clinical Data to Assess Diagnosis*, was found through Kaggle, a repository of community collected and published data.[17] This dataset contained anonymized data from Hospital Sírio-Libanês, São Paulo, Brazil. All data was previously normalized and scaled by column according to a min/max scaler to fit between -1 and 1. The data set provided minimum, maximum, mean, and medium values for each original feature in the data, but in the case of this study, only mean values and/or binary values were studied. This study observed a total of 383 samples.

To begin the analysis, the data was first preprocessed using the Pandas software library. The study assumed a missing completely at random model for the missing data points. With this assumption, missing values were filled with mean values from available samples. Two data points, for patients with ID = 199 and ID = 287 had values listed as 'NaN', so those patient details were disregarded.

Causal Assumptions

In the narrowed analysis of the effects of the counts of the five aforementioned blood factors on ICU admission, several causal assumptions were made based on outside research. The factors presented in Figure 1a were not all observed in this study and were identified based on outside research. Figure 1b narrows down influential factors to those that were available to be observed in this study.

a.



b.

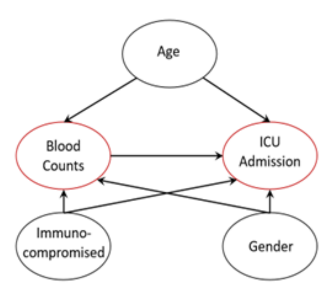


Figure 1. Causal graph of all predicted factors (a), causal graph of available/studied factors (b) in the relationship between blood counts and ICU admission

Methods

In the dataset, an ICU admission datapoint of '0' expressed a lack of admission while a datapoint of '1' equated to admission of the patient. Using this binary scale, a random forest classifier was applied to determine ICU admission or no ICU admission for patients first based on all relevant covariates - hemoglobin, leukocyte, lymphocyte, neutrophil, and platelet counts, body temperature, age, gender, and immunocompromised/not immunocompromised status. Then, the study focused more directly on blood factors, exploring their lesser-known role in COVID-19 infection. Once again, a random forest classifier was produced to determine ICU admission status using only the counts of the five blood factors - hemoglobin, leukocytes, lymphocytes, neutrophils, and platelets.

Feature Importance

Core analysis in this study centered around determining feature importance in various random forest classifiers. A random forest classifier essentially trains and tests data points using a set of decision trees that take features, or independent variables, into account to determine a dependent outcome. Feature importance is calculated for such a classifier by determining how useful each feature is in determining the final outcome. Algorithms calculate each feature's importance by measuring the decrease in accuracy when a given feature's values are randomly permuted. If the decrease in accuracy is low, the feature is not extremely important, while if the decrease in accuracy is high, the feature is more important. [18]

Tools

The analysis of ICU admission in patients with COVID-19 was performed using the Python language with the Microsoft Visual Studio Code platform, Scikit-learn, and Pandas. Seaborn and Matplotlib packages were used for data visualization.

Results

All Factors

Computational models to predict ICU admission were developed. To begin the analysis, pairwise plots of data relating ICU admission to relevantly deemed covariates (the counts of hemoglobin, leukocytes, lymphocytes, neutrophils, and platelets, as well as body temperature, age, gender, and immunocompromised status) were plotted (Figure 2).

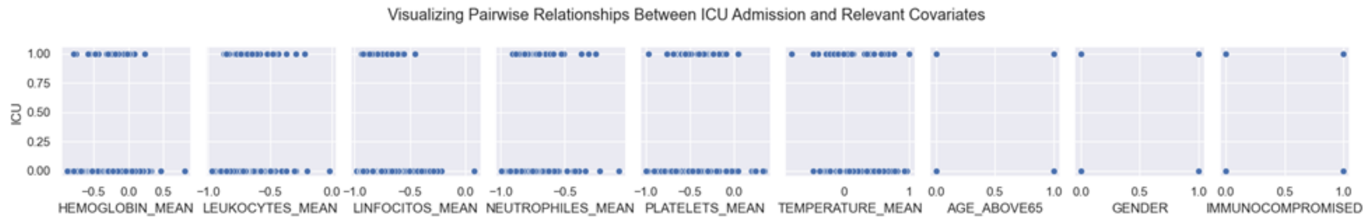


Figure 2. Pairwise plots of all studied covariates (hemoglobin, leukocyte, linfocito, neutrophil, and platelet counts, body temperature, age, gender, and immunocompromised/not immunocompromised status) against ICU admission.

The plots in Figure 2 determined that a relationship was present between ICU admission and each covariate, prompting the continuation of study for all factors.

Following this preliminary analysis, machine learning models were developed to predict likelihood of ICU admission based on previously stated covariates. A random forest classifier was developed to fit the data, which was successful to a 93.047% accuracy (+ or – 2%). The importances of each covariate in determining ICU admission according to this model is visualized below (Figure 3).

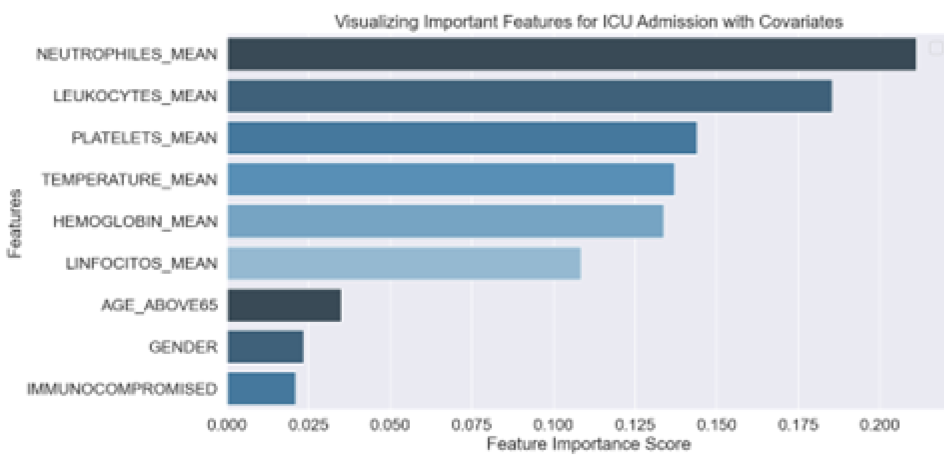


Figure 3. Bar plot ranking importance of each studied covariate in determining ICU admission in the random forest classifier

Figure 3 revealed that the counts of three of the observed blood types - neutrophils, leukocytes, and platelets - were the most important in determining ICU admission. According to the model, age, gender, and immunocompromised status, had the least impact on ICU admission in order from most to least influential.

Blood Factors

Due to how blood factors are relatively understudied in relation to COVID-19 infection severity, this study narrowed its focus to also examine the relationship exclusively between the five previously observed blood factors and ICU admission. To do this, another random forest classifier was run, comparing the blood factors and ICU admission. This classifier yielded a 92.174% accuracy (+ or – 5%). This classifier was used to observe the importance of each blood factor on ICU admission (Figure 4).

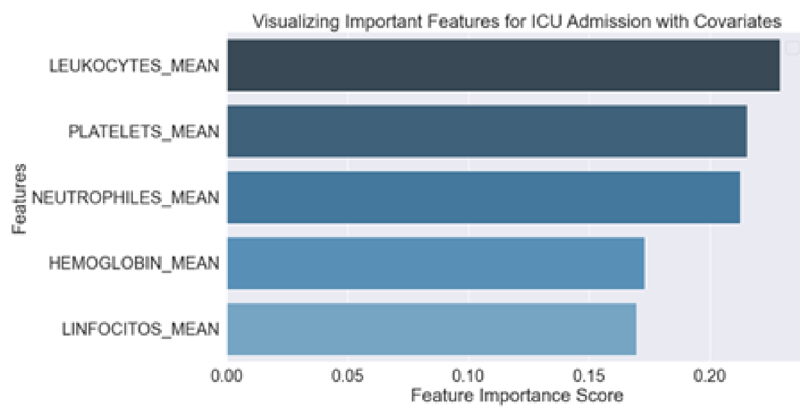


Figure 4. Bar plot ranking importance of each blood factor in determining ICU admission in the random forest classifier

Figure 4 demonstrated that of the five blood types, leukocyte counts played the largest role in determining ICU admission, followed by platelet and neutrophil counts. Lymphocyte counts had the least impact in determining ICU admission vs. no admission.

Discussion

The model demonstrated that neutrophil, leukocyte, and platelet counts were the most important features in determining ICU admission, while the covariates of age, gender, and immunocompromised status had the least impact on determining ICU admission in patients with COVID-19.

Analysis

When ranking the importance of all nine covariates in their importance to determining ICU admission in patients with COVID-19, neutrophil counts were the most important, while immunocompromised status was the least important. Considering that neutrophils are the body's main effector cells that function in the immune system to combat infectious agents, it is logical that the counts of these cells would reflect sickness severity and therefore ICU admission

– as a person's sickness increases in severity, the body creates more white blood cells, like neutrophils, to combat pathogens. [19,20]

The low importance of three covariates - gender, age, and immunocompromised status - on ICU admission in this study was curious, as these factors are widely accepted as significant factors in determining virus severity and mortality. This finding demonstrates that blood factors, which are less studied in their relation to COVID-19, may have a greater influence than these widely accepted factors in determining COVID-19 severity.

Related results

A key result of this study - the finding that age, gender, and immunocompromised status were less important in determining ICU admission than blood counts - was especially interesting.

Age-wise, studies have demonstrated that elderly patients exposed to COVID-19 are more likely to experience severe infection, and/or death. [21] Over 81% of COVID-19 deaths occur in people over age 65, and the number of deaths among those over age 65 is 97 times higher than the number of deaths among people aged 18-29 years. [22] Other studies have corroborated this, also presenting that the risk of the severe COVID-19 was significantly higher in midlife and older adults compared to young adults. [23] Severe COVID-19 may logically correlate to ICU admission.

In terms of gender, a growing body of literature presents that infectious diseases may impact women and men at different extremities. A 2020 study presented that there is a sex bias in COVID-19, especially at the early stage of the disease, with women having an advantage in defense against the virus. [24] This disparity in immune response has also been shown to correlate with health outcomes. For example, mortality due to COVID-19 is twice as common in males than females.[25] Another study demonstrated that intensive care was required more often for men of all ages than for women.[23] This reasons that males are more susceptible to severe COVID-19, which may lead to increased ICU admission rates for males than females.

Past research has also demonstrated that immunocompromised persons are at increased risk for severe COVID-19–related outcomes, including hospitalization, ICU admission, ventilator use, and death. [26,27]

The findings of this study are curious in respect to this past research, as it shows that these three supposedly key factors - gender, age, and immunocompromised status - are less influential to COVID-19 severity (specifically to ICU admission for COVID-19 infection) than other variables, like blood factors. Further exploration into blood may present new, potentially more accurate, methods of predicting COVID-19 severity in patients apart from these three currently well-studied features.

Limitations

A key limitation of the study was in relation to the available data. Only 383 samples were processed in this study, which is a relatively small amount of data. Potentially more accurate results may be yielded with a larger dataset. Another limitation was the scaled nature of the data. This allowed a less accurate analysis, especially in terms of analyzing body temperature and fever in patients with COVID-19, as there was no way to exactly determine the correct threshold for fever/no fever. A raw, unscaled dataset may allow for a more exact determination of the influence of body temperature in patients with COVID-19 in relation to the various independent factors.

Another key limitation of the study was imbalanced data. When analyzing ICU admission, the study observed 351 samples of negative ICU admission, compared to only 32 samples of positive ICU admission. While this variance in counts of positive vs. negative outcomes is reflective of the real world, the imbalance could have skewed accuracy metrics when the data was run through random forest classifier models.

Finally, it is not clear whether the verification of SARS-CoV-2 infection with nasal and pharyngeal swab is performed properly for each studied patient, or if all data was collected properly and exactly. This can be a source of false positive or negative findings.

Conclusion

Applications

With the results of this study, doctors and other health professionals can use counts of various blood factors, in parallel with or separate from basic relevant covariates (age, gender, immunocompromised status) to predict severity of COVID-19 in hospitalized patients. This will allow them to prepare necessary supplies and materials for care in advance (i.e., ICU beds, ventilators, etc.).

Future Work

In the future, this study could be repeated with a larger, unscaled dataset. It could also be useful to experiment with balanced datasets that evenly reflect positive and negative outcomes. This could yield more accurate results and validate the findings of this study.

Due to the unexpectedly high importance of blood types in determining ICU admission in patients with COVID-19, more thorough analysis could also be performed on a wider range of blood factors to explore how, why, and what blood factors influence severity of COVID-19. It could also be valuable to analyze the counts of blood factors over different time frames in a patient's hospital stay to observe how blood counts vary with worsening of infection and infection recovery.

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