Bernat Sort Rufat

Development and evaluation of a new non-invasive and high sampling rate score to assess lung injury for ventilated patients

Degree Final Project

Conducted by Dr. Josep Gómez Álvarez

Conducted by Dr. Roger Guimerà Manrique

Supervised by Dr. Alejandro Rodríguez Oviedo

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Abstract

Nowadays, the gold standard measurement to assess the level of lung failure in critically ill patients in the intensive care unit (ICU) is the respiratory Sequential Organ Failure Assessment (SOFA) score, which takes values from 0 (no failure) to 4 (maximum failure). This method is based on partial pressure of oxygen in arterial blood (PaO_2) measurements through its relationship with the fraction of inspired oxygen (FiO_2): the PaO_2/FiO_2 ratio. While FiO_2 can be obtained non-invasively and at a high sampling rate, obtaining PaO_2 is carried out by an invasive and punctual technique at a low sampling rate. This project aims to develop and evaluate a new non-invasive and high sampling rate score based on pulse oximeter oxygen saturation (SpO_2) to assess lung injury for ventilated patients.

This study gathered clinical data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database of patients who were admitted to the ICU for whom the SOFA score was calculated. The daily frequency of PaO_2 values was compared to the daily frequency of SpO_2 values to see the sampling rate of each method. The nonparametric rank correlation method Spearman's rho test was used to measure the correlation between the PaO_2/FiO_2 and SpO_2/FiO_2 ratios. The new respiratory score was developed based on the SpO_2/FiO_2 ratio's descriptive statistics such as median, quartile 1, and quartile 3. Patients with a respiratory SOFA score of 4 (maximum score) that showed differences between the new respiratory score based on the SpO_2/FiO_2 and the gold standard respiratory SOFA score were enrolled in evaluating if the new score performed better than the gold standard when it came to predicting mortality. That data was randomly divided and assigned into a training set and a test set. Six machine learning algorithms for classification were used to develop that task. The area under the curve (AUC) of both methods was compared to see which one performed better when it came to predicting mortality.

Results demonstrated that the daily frequency of PaO_2 values is low while SpO_2 is an automated methodology for monitoring lung damage at a high sampling rate. The nonparametric rank correlation method Spearman's rho test showed a good or moderate correlation of 0.653793 between the PaO_2/FiO_2 and SpO_2/FiO_2 ratios. The groups for the new respiratory score based on the SpO_2/FiO_2 ratio were set from above 245 for the score 0, from 235 to 250 for the score 1, from 196 to 247.5 for the score 2, from 158.33 to 200 for the score 3, and under 132.85 for the score 4. A total of 8587 patients were finally enrolled in evaluating if the new score performed better than the gold standard when it came to predicting mortality. They were randomly split into a training set (6011, 70%) and a test set (2576, 30%). Results indicate that both methods perform similarly when predicting mortality as the machine learning models showed similar AUC values (ranging from 0.60 to 0.68) for both approaches.

The new score based on the SpO_2/FiO_2 ratio predicts mortality and assesses lung failure in a similar way to the gold standard method and could surrogate it due to the advantage that it is a non-invasive method at a high sampling rate.

Keywords: Sequential Organ Failure Assessment (SOFA); respiratory SOFA score; PaO_2/FiO_2; SpO_2/FiO_2; lung injury; mechanical ventilation; non-invasive and high sampling rate score; intensive care; big data; data science; machine learning.

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1 Introduction

Critically ill or injured patients need a higher degree of specialized care than inpatients. Thus, they are admitted to the intensive care unit or ICU.

An ICU is a multidisciplinary and access-restricted area designed for the provision of intensive and specialized care by means of monitoring and life support systems to critically ill patients with or at risk of developing acute organ dysfunction, that requires surveillance and personalized treatments [1],[2]. The ICU provides support to failing organ systems, such as the lungs, cardiovascular system, and kidneys through mechanical ventilation, monitors, and dialysis machines [2].

Overall, the goal of intensive care is to provide the best care for patients maintaining vital functions in order to prevent physiological deterioration, reduce mortality and prevent morbidity in critically ill patients [3].

In the past few years, health information technology has enabled a quantum leap in the way tasks are done. In the United States, thanks to the signing of the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009, the legislation provided financial incentives for providers to implement health information technologies and financial penalties for those who did not [4].

In 2008 only 9% of United States hospitals and 17% of physicians utilized an electronic health record (EHR) [4]. As of 2015, this had increased to 96% of hospitals and 78% of physician offices [4],[5]. Therefore, all paper-based information has been transferred to an electronic medical record and EHR adoption is widespread across most hospitals and at the state level [5]. This is essential to be able to collect all patient information so that it is available to doctors in a clear, correct, and complete way so that they can make decisions on how to treat patients.

As healthcare has digitized, the amount of information contained in electronic healthcare records has exploded [6] and this has resulted in a deluge of clinical big data and has prompted the rapid growth of data science and machine learning (ML) in medicine [7]. The ICU brings the opportunity for using data science to improve patient care due to the availability of providing large amounts of data [7]. This is the reason some institutions with very large clinical databases which seek to endorse clinical research in the intensive care setting, have placed them at the disposal of investigators throughout the world [8].

One of the most popular initiatives is the Medical Information Mart in Intensive Care (MIMIC-IV) launched by the Beth Israel Deaconess Medical Center (BIDMC), a large and publicly accessible database that comprises deidentified health-related data associated with over 70000 patients who stayed in critical care units [6].

In the intensive care unit (ICU) severity scales are important adjuncts of treatment because they allow to score the gravity of an illness and classify it in a systematic and internationally accepted way. They are useful to predict patient outcomes, compare the quality of care and stratify for clinical trials [9].

Moreover, using scores allows having a systematic nomenclature that will be very important when it comes to exploiting data. There are several ICU scoring systems such as acute physiology and chronic health evaluation (APACHE II) [10] and Sequential Organ Failure Assessment (SOFA) [9].

In this project, we focused on the SOFA scoring system. In 1994 the European Society of Intensive Care Medicine (ESICM) organized a consensus meeting in Paris to create a so-called sepsis-related organ failure assessment (SOFA) score, further revised in 1996 [11].

The Sequential Organ Failure Assessment or SOFA score was developed "to describe quantitatively and as objectively as possible the degree of organ failure over time in groups of patients or even individual patients" [11] and was based on six different scores, one for each of the respiratory, renal, hepatic, cardiovascular, hematological, and neurological systems. Each one of them scored from 0 to 4 with an increasing score reflecting worsening organ dysfunction [12].

For the purpose of this project, we focused on the respiratory SOFA score. As mentioned before, the SOFA score is the sum of six sub-SOFA categories, in which the respiratory is one of the most important ones as more than half of critically ill patients require mechanical ventilation for respiratory support [13], one of the most common interventions in ICUs. That is because lung injured patients with acute respiratory failure, representing more than fifty percent of the patients in ICU, are ventilated the first 24 hours after admission [13].

Assessment of the respiratory SOFA score is based on the ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen [14], the PaO_2/FiO_2 ratio (expressed in mmHg) [12]. PaO_2/FiO_2 ratio is one of the main and most popular ratios to determine and classify the degree of hypoxemia through arterial blood gases [15].

As previously mentioned, the respiratory SOFA score calls for patients to receive a score from 0 to 4 depending on the severity of the disease based on the PaO_2/FiO_2 ratio, as described below in Table 1.

Table 1. The criteria for assessment of the respiratory SOFA score [12].

Respiratory system	
PaO_2/FiO_2 (mmHg)	SOFA score
> 400	0
< 400	1
< 300	2
< 200 with respiratory support	3
< 100 with respiratory support	4

Accordingly, on the one hand, the respiratory SOFA score relies on the partial pressure of oxygen in arterial blood (PaO_2), which is the pressure exerted by oxygen on the arterial walls, expressed in mmHg [16] and measures how well oxygen is able to move from the lungs into the blood [17]. On the other hand, it relies on the fraction of inspired oxygen (FiO_2) expressed as a fraction, not a percentage [18], which is the fractional concentration of oxygen in the inspired gas mixture [19]. The concentration of oxygen in room air is 21%, therefore, the fractional percentage of inspired oxygen or FiO_2 is 0.21 [15].

Monitoring the patient is essential to improve patients' survival and care and can be invasive or non-invasive [20]. However, invasive monitoring such as arterial blood gas (ABG) analysis may cause discomfort to the patient due to the intra-arterial catheter or the repeated needle punctures to obtain the samples, which cause blood loss and can spread infection [21].

Nowadays, PaO_2 is the gold standard to assess acute hypoxic respiratory failure [22]. However, to obtain PaO_2 an arterial blood gas (ABG) test is required which is an invasive method because the test uses blood obtained with an arterial puncture using a needle [23].

Moreover, it is only routinely available by intermittent spot checks, precluding any automatic, accurate, and continuous evaluation or analysis [22].

Therefore, there are limitations in using the PaO_2/FiO_2 ratio to assess lung failure. Additionally, institutions are making an effort to contain costs, conserve blood and minimize the inappropriate use of this method, significantly reducing the number of arterial blood gas samples obtained in mechanically ventilated patients [24].

For all the aforementioned reasons, there is a trend toward searching for minimally invasive methods to assess lung failure [25].

Measuring and monitoring oxygen saturation levels play an important role in assessing the respiratory status of critically ill patients in ICUs [26].

Pulse oximeter oxygen saturation (SpO_2) [18] also known as peripheral oxygen saturation measured by pulse oximetry is the percentage of hemoglobin saturated with oxygen in arterial blood measured by pulse oximetry [27],[25]. Pulse oximetry is a simple, cheap, continuous, noninvasive, and routine standard monitoring method used in ICUs to measure SpO_2 [27],[28],[29]. Pulse oximeters use a sensor that when placed on the finger can monitor the amount of oxygen in the blood [28]. Therefore, it can be obtained rapidly, and it does not require blood gas testing [25].

All things considered, we thought that SpO_2 could be a good candidate to surrogate PaO_2 and for developing a new score of lung failure using the SpO_2/FiO_2 ratio based on the gold standard respiratory SOFA score.

2 Hypothesis and objectives

Nowadays, the gold standard measurement to assess the level of lung failure is the respiratory SOFA score, which is based on an invasive method at a low sampling rate.

Our hypothesis is that this gold standard method to assess the level of lung failure could be surrogated by a non-invasive and at a high sampling rate SpO_2-based approach.

In order to prove our hypothesis and accomplish our goal, we have set specific aims, which are:

- Implement an Extraction, Transform and Load (ETL) process to obtain a ready-to-analyze dataset from the latest update of the Medical Information Mart for Intensive Care database (MIMIC-IV).
- Characterize the relationship between the SpO_2/FiO_2 ratio and the PaO_2/FiO_2 ratio.
- Develop a new score of lung failure using the SpO_2/FiO_2 ratio based on the gold standard respiratory SOFA score.
- Evaluate the performance of the new score against the gold standard using a battery of ML classification algorithms to predict mortality.

3 Methods

3.1 MIMIC-IV database

The Medical Information Mart for Intensive Care (MIMIC-IV), an update to the MIMIC-III database, is a relational database comprising comprehensive clinical information from 2008 to 2019 on real hospital stays for over 70000 patients [6] admitted to a tertiary academic medical center in Boston, MA, USA [30].

It is sourced from two in-hospital database systems in Beth Israel Deaconess Medical Center: a custom hospital-wide Electronic Health Care Record (EHR) and an ICU-specific clinical information system [31].

The database is intended to support a wide variety of research in healthcare. For this purpose, comprehensive patient information such as vital signs documented, laboratory measurements, and medications administered in the hospital are contained in the MIMIC-IV database [32].

MIMIC-IV is grouped into several modules to reflect the provenance of the data, including *core*, *hosp*, and *icu* modules. The *core* module contains patient stay information (i.e., admissions and transfers) and the *hosp* module contains hospital-level data for patients: labs, micro, and electronic medication administration. The *icu* module contains ICU level data, the event tables, which contain a stay_id column allowing identification of the associated ICU patient in icustays, and an itemid column allowing identification of the concept documented in d_items [31].

3.1.1 Getting access to the MIMIC-IV database

As MIMIC-IV is a restricted-access resource available from PhysioNet, to access the files we had to fulfill some requirements.

First of all, you need to become a credentialed user on PhysioNet. In order to become a credentialed PhysioNet user and access the restricted-access clinical databases, you must complete a suitable training program in human research subject protections and HIPAA regulations [33]. So, we completed the Collaborative Institutional Training Initiative (CITI) Program's "Data or Specimens Only Research" course (see Appendix 2).

Once we finished the required training, we signed the Data Use Agreement (DUA) to access the files and got access to the MIMIC-IV database.

3.2 Tools

3.2.1 Using the Cloud

Nowadays, the MIMIC-IV database is available on the Google Cloud Platform (GCP). Therefore, there is no need to set up a local database or bring up a local Jupyter instance. Instead, we connected to a BigQuery client with our Google Cloud project.

The fact that all datasets are hosted on GCP has many advantages. On the one hand, it allows maintainers to control data access, update databases on an ongoing basis and ensure new code and new tables are being developed. On the other hand, researchers have access to the last database update without needing to download anything locally and can query datasets using Google's serverless data warehouse called BigQuery [34]. Therefore, we created a GCP account in order to access the desired datasets and run queries for our project.

3.2.2 Querying data in BigQuery

In order to extract data from the source system (the MIMIC-IV database), we used Structured Query Language (SQL) since MIMIC-IV data is hosted in Google's serverless data warehouse called BigQuery, described by Google as "a fully managed enterprise data warehouse that helps you to manage and analyze your data through SQL queries" [35].

We created a project within Google Cloud Console and enabled our BigQuery API for the selected project. Then, we created a service account and configured it via IAM to access BigQuery within our project. Finally, we added BigQuery permissions to our new service account and enabled Google Cloud Billing [36]. Once connected to a BigQuery client with the desired Google Cloud project, we were able to run queries using BigQuery.

3.2.3 Google Colaboratory

We worked with Google Colaboratory or "Colab" for short, a free cloud service hosted by Google that allows us to write and execute Python code through the browser providing a serverless Jupyter notebook environment for interactive development with tremendous computational power [37].

It is useful and well suited to machine learning, data analysis, and Artificial Intelligence research [38],[39].

3.3 Cohort and variable selection

We included patients from the MIMIC-IV database who were admitted to the ICU and for whom the SOFA score was calculated.

Data was collected on an hourly basis since the SOFA score is calculated for every hour of the patient's ICU stay. That is why the initial dataset did not contain a row per patient but a row for each patient and its hour relative to admission. This resulted in a very large dataset.

However, the initial dataset did not contain all the information we needed for our project. Therefore, we included the variables listed in Table 2 aggregated by hour relative to admission.

There were cases where SpO_2, PaO_2, and FiO_2 measurements were collected more than once in a specific hour. In order to select one measurement per hour, we applied the following criteria:

- We kept the smallest SpO_2 value because low oxygen saturation, defined as $SpO_2 \leq 95\%$, is associated with mortality caused by pulmonary diseases [40].
- We kept the smallest PaO_2 value because a $PaO_2 < 80$ mmHg indicates hypoxemia [41].
- We kept the largest FiO_2 value. A PaO_2/FiO_2 ratio ≤ 300 mmHg indicates hypoxemia [42]. Therefore, when calculating the PaO_2/FiO_2 ratio, the larger the FiO_2, the worse.

Table 2. Variable selection. The criteria for assessment of the respiratory SOFA score [12].

Variables	Description	MIMIC-IV Dataset	Unit of measurement
SpO_2	Pulse oximeter oxygen saturation	vitalsign	Percentage
PaO_2	Partial pressure of oxygen in arterial blood	chartevents	mmHg
FiO_2	Fractional percentage of inspired oxygen	ventilator_settings	Percentage
hospital_expire_flag	Indicate if the patient died during a specific hospital stay	icustay_detail	

3.4 Data cleaning

3.4.1 Outlier detection and removal

After checking the distribution of SpO_2, PaO_2, and FiO_2 variables using histograms, we removed values less than or equal to zero due to their lack of biological sense.

To handle outliers, as our data distribution was skewed, we used the Interquartile Range Technique [43] to detect and remove them afterward. Once this was done, our variables were in a consistent biological range.

3.5 Data imputation

Before performing any analysis, we had to handle missing data.

First, we checked if PaO_2 records were collected at a lower sampling rate than the SpO_2 records. This was achieved by comparing the daily frequency of PaO_2 records per patient versus the daily frequency of SpO_2 records per patient using violin plots.

Then, for each patient we forward-filled SpO_2, PaO_2, and FiO_2 missing values replacing them with the value from the previous row.

Previous procedures such as outlier detection and removal, treatment of missing values, and feature engineering were fundamental in order to have a more complete and well-structured data frame.

3.6 Creation of the PaO_2/FiO_2 and SpO_2/FiO_2 ratios

For each patient, we calculated both SpO_2/FiO_2 and PaO_2/FiO_2 ratios and added them to our dataset.

The SpO_2/FiO_2 ratio, also known as the SpFi ratio, was calculated as:

$$\text{SpFi} = \left(\frac{SpO_2}{FiO_2}\right) \cdot 100 \tag{1}$$

The PaO_2/FiO_2 ratio, also known as the PaFi ratio, was calculated as:

$$\text{PaFi} = \left(\frac{PaO_2}{FiO_2}\right) \cdot 100 \tag{2}$$

3.7 Correlation between PaO_2/FiO_2 and SpO_2/FiO_2 ratios

To test if both PaFi and SpFi followed a normal distribution, we used the Jarque – Bera normality test. This test determines whether or not sample data have skewness and kurtosis that matches a normal distribution, and it is appropriate for large samples [44],[45].

To measure the strength and direction (negative or positive) of association between the PaO_2/FiO_2 and SpO_2/FiO_2 ratios [46], we used Spearman's Rank correlation coefficient, which is a non-parametric statistic test, and hence it does not rest upon an assumption of normality [47].

3.8 Creation of the new respiratory SOFA score

To develop a new score of lung failure using the SpO_2/FiO_2 ratio based on the gold standard respiratory SOFA score, we went through several steps.

The first thing we did was to delete all rows in our dataset which contained PaFi and SpFi null values.

Next, we created the respiratory SOFA PaFi label, based on the criteria for assessment of the respiratory SOFA score shown in Table 1.

Once we created the respiratory SOFA PaFi label, we could display the SpFi distribution based on each respiratory SOFA PaFi score using boxplots.

Finally, considering the SpFi descriptive statistics such as median, quartile 1, and quartile 3, we generated the groups (0, 1, 2, 3, and 4) of the new respiratory SOFA score based on the SpO_2/FiO_2 ratio.

3.9 Datasets for the evaluation of ML algorithms

Once we developed a new score of lung failure using the SpO_2/FiO_2 ratio based on the gold standard respiratory SOFA score, we needed to evaluate the performance of the new score against the gold standard using a battery of ML classification algorithms to predict mortality.

The dataset for the evaluation only contained those rows that showed differences between the SOFA SpFi score and the SOFA PaFi score, to see if this difference affected the prediction of mortality.

To justify that lung damage might be related to mortality we kept only those patients that at some point had a respiratory SOFA PaFi score of 4 since it represents the highest degree of organ failure or dysfunction and hence it is associated with mortality.

We compacted the dataset into one row per patient, containing whether the patient died during a specific hospital stay or not and the percentage of each respiratory SOFA score (both respiratory SOFA scores based on PaFi and based on SpFi), representing the percentage that each patient had spent in each stage of the respiratory disease (0, 1, 2, 3, and 4) during their ICU stay.

Furthermore, we added confounders such as the age and the Oxford Acute Severity of Illness Score (OASIS) [48] for each patient to adjust our model for patients' age and severity of illness.

Finally, we divided the dataset according to whether it contained respiratory SOFA score based on PaFi or SpFi. Table 3 and Table 4 show an example of the structure of both datasets.

Table 3. Features and target dataset example of PaFi on subset srpafi4% > 0*

hospital_expire_flag	srpafi4%	srpafi3%	srpafi2%	srpafi1%	srpafi0%	oasis	age
1	1.2	28.1	35.9	31.9	2.8	45	56
0	9.1	34.8	37.9	18.2	0.0	39	72
0	1.6	7.8	41.4	29.9	19.3	44	83
1	1.8	40.0	41.0	11.7	5.5	38	77

* SOFA based on PaFi on subset where patients had SOFA PaFi of 4 and showed differences between the new SOFA SpFi and the gold standard SOFA PaFi.

Table 4. Features and target dataset example of SpFi on subset srpafi4% > 0*

hospital_expire_flag	srspfi4%	srspfi3%	srspfi2%	srspfi1%	srspfi0%	oasis	age
1	0.9	1.6	0.3	1.6	95.6	45	56
0	12.1	33.3	19.7	3.0	31.8	39	72
0	4.5	34.4	14.8	37.3	9.0	44	83
1	3.8	39.9	15.9	15.2	25.3	38	77

* SOFA based on SpFi on subset where patients had SOFA PaFi of 4 and showed differences between the new SOFA SpFi and the gold standard SOFA PaFi.

3.10 Data splitting

We transformed our data into a binary classification problem. First, we separated the independent variables from the dependent variable. Feature columns were the percentage of each respiratory SOFA score that each patient had spent in each stage of the respiratory disease, and the age and OASIS confounders. The fact that patients died or survived during their ICU stay was set as the target column.

Before feeding the data into any machine learning algorithm, it is important to split it so that we can see how well the model performs on data that is not training on and avoid overfitting. Therefore, we divided the dataset into two subsets: the training set, used to fit the ML model, and the test set, used to evaluate the trained ML model [49]. We put 70% of the data in the training set and 30% of the data in the test set. As we were classifying an imbalanced dataset, we applied stratified splits in order to have the same percentage of samples of each class in the training and test sets [50]. All algorithms we implemented considered the same data splitting.

3.11 Oversampling using the Synthetic Minority Oversampling Technique (SMOTE)

As we dealt with imbalanced data, our model might try to fit the majority class and provide a biased prediction, as well as give misleading accuracy.

For that reason, after splitting the data, we performed an oversampling procedure on the minority class (patients who died) of the training set with SMOTE [51].

3.12 Machine learning algorithms for classification

We implemented six different machine learning algorithms on our datasets to evaluate if the new score performed better than the gold standard when it came to predicting mortality.

The ML algorithms for classifications that we implemented were logistic regression [52], random forest [53], k-Nearest Neighbors (KNN) [54], Support Vector Classifier (SVC) [55], and boosting algorithms, including Adaptive Boosting (AdaBoost) [56] and Extreme Gradient Boosting (XGBoost or XGBC) [57].

3.13 Evaluation of the ML algorithms for classification

We used the area under the ROC (Receiver Operating Characteristics) curve metrics (AUC) [58],[59] for evaluating our ML algorithms. Then, we compared the PaFi and SpFi AUCs obtained by the ML algorithms for classification to see which method performed better when it came to predicting mortality.

4 Results and discussion

4.1 Participants

A total of 76540 ICU patients from the MIMIC-IV database were screened for eligibility. Of these 76540 patients, 21 were excluded due to the lack of SOFA score, 39 patients were excluded after removing SpO_2, PaO_2, and FiO_2 values less than or equal to zero, and 47989 patients were excluded after removing rows that contained PaFi or SpFi null values.

In order to evaluate the performance of the new score against the gold standard when predicting mortality, patients that showed no differences between the respiratory SOFA PaFi score and the respiratory SOFA SpFi score (933 patients), and patients that never had a respiratory SOFA PaFi score of 4 (18971 patients) were also excluded from our study. Finally, 8587 patients were eligible for participation.

A flowchart of the patients analyzed in this study and the different steps applied in each cohort is shown in Fig. 1.

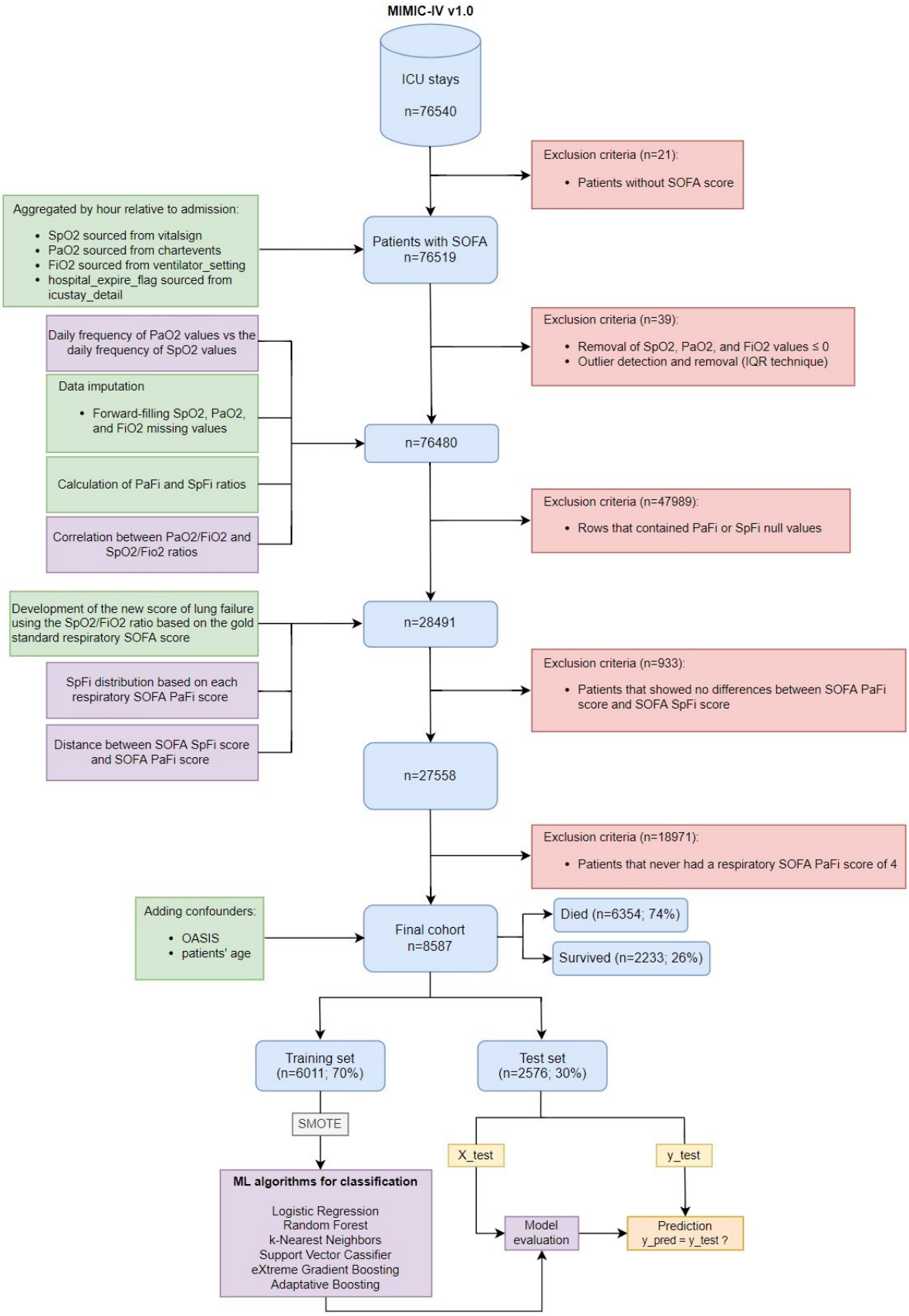

Figure 1. Flowchart of this study. This flowchart shows the patient selection and the different steps applied in each cohort.

4.2 Daily frequency of PaO_2 values vs the daily frequency of SpO_2 values

We found that PaO_2 was obtained at a median of 1.3 times per day for each patient while SpO_2 was obtained at a median of 23 times per day for each patient. That is to say, almost one SpO_2 register per hour. Therefore, PaO_2 records were collected at a lower sampling rate than the SpO_2 records, as shown in Fig. 2. This is because PaO_2 is an invasive method obtained through an ABG test, precluding continuous monitoring. Hence, sampling resolution is low.

Therefore, our results demonstrated that SpO_2 is an automated methodology for monitoring lung damage at a high sampling rate.

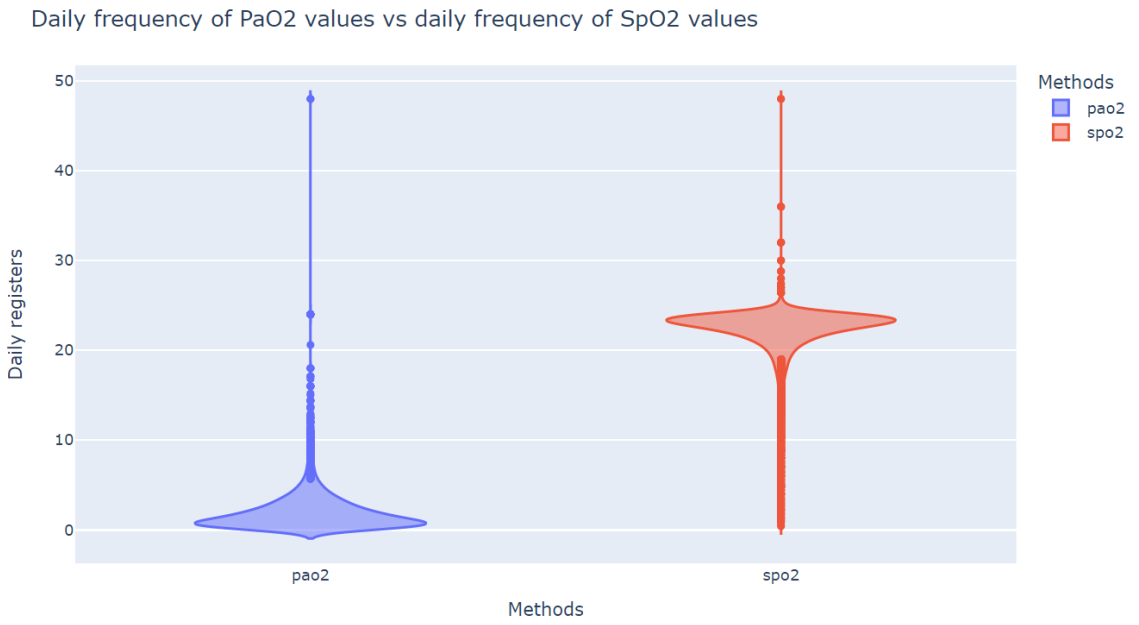

Figure 2. Daily frequency of PaO_2 records per patient versus the daily frequency of SpO_2 records per patient.

4.3 Correlation between PaO_2/FiO_2 and SpO_2/FiO_2 ratios

Since the Jarque – Bera normality test for both PaFi and SpFi showed a p-value ≤ 0.05, we assumed neither PaFi nor SpFi followed a normal distribution.

The nonparametric rank correlation method Spearman's rho test showed a correlation of 0.653793 between the PaO_2/FiO_2 and SpO_2/FiO_2 ratios, as shown in Fig. 3. Therefore, there is a moderate or good correlation [60],[61] between the PaO_2/FiO_2 and SpO_2/FiO_2 ratios, with clear statistical evidence that the observed relationship is not due to chance (p-value = 0.0).

Figure 3. Correlation between PaO_2/FiO_2 and SpO_2/FiO_2 ratios.

4.4 SpFi distribution based on each respiratory SOFA PaFi score and generation of groups of the new respiratory SOFA score based on the SpO_2/FiO_2 ratio.

The new score is grouped as described below. Patients receive a score of 0 if they reach a SpO_2/FiO_2 ratio greater or equal to 245. If patients reach a SpO_2/FiO_2 ratio less than 250 and greater or equal to 235, less than 247.5 and greater or equal to 196, or less than 200 and greater or equal to 158.33, they receive a score of 1, 2, or 3, respectively. The highest degree of organ failure or dysfunction is represented by a score of 4 when patients reach a SpO_2/FiO_2 ratio of less than 132.85.

The SpFi distribution based on each respiratory SOFA PaFi score is shown in Fig. 4. The groups (0, 1, 2, 3, and 4) we generated of the new respiratory SOFA score based on the median, quartile 1, and quartile 3 of the SpO_2/FiO_2 ratio are shown in Fig. 5.

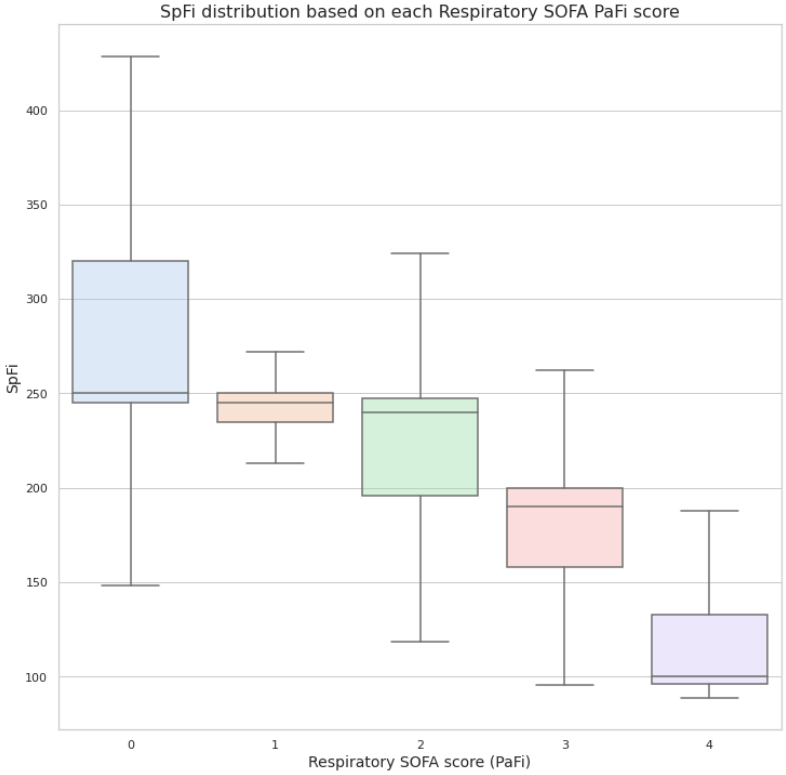

Figure 4. SpFi distribution based on each respiratory SOFA PaFi score.

sofa_pafi	spfi					
	min	max	mean	median	q25	q75
0	148.333333	500.000000	271.144949	250.0	245.000000	320.000000
1	111.250000	495.000000	247.475897	245.0	235.000000	250.000000
2	89.000000	495.000000	227.090685	240.0	196.000000	247.500000
3	89.000000	476.190476	184.285342	190.0	158.333333	200.000000
4	89.000000	466.666667	120.944177	100.0	96.000000	132.857143

Figure 5. Groups (0, 1, 2, 3, and 4) of the new respiratory SOFA score based on the SpO_2/FiO_2 ratio.

4.5 Distance between SOFA SpFi score and SOFA PaFi score

The histogram shown in Fig. 6 shows the differences between the SOFA SpFi score and the SOFA PaFi score.

We observe that the difference between the SOFA SpFi score and the SOFA PaFi score is mostly 0, meaning that the SOFA PaFi score and the SOFA SpFi score coincide.

However, we were only interested in the differences, as the dataset for the evaluation only contained those rows that showed differences between the SOFA SpFi score and the SOFA PaFi score, to see if this difference affected the prediction of mortality.

As we took the SOFA SpFi score as a reference when calculating the difference (3), a difference of -1 means that we are assigning to the patient a more minor score than the one he actually has, insinuating that the patient is in better conditions than he actually is. On the other hand, a difference of 1 means that we are assigning to the patient a higher score than the one he actually has, insinuating that the patient is in worse conditions than he actually is, and so forth.

$$\text{Distance} = \text{SOFA SpFi score} - \text{SOFA PaFi score} \quad (3)$$

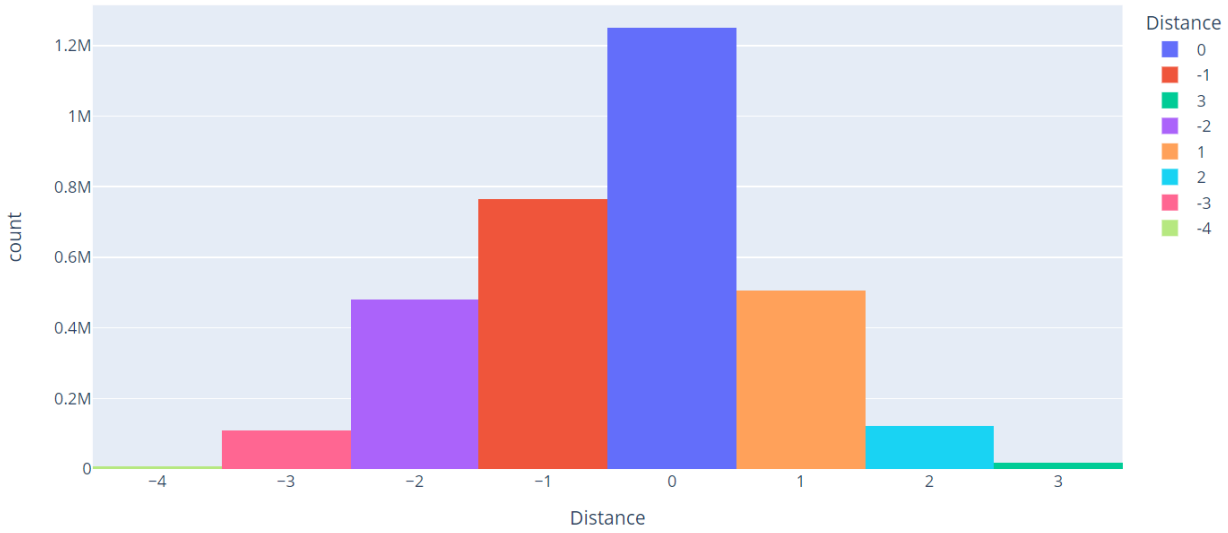

Figure 6. Histogram showing the distance between SOFA SpFi score and SOFA PaFi score.

4.6 PaFi vs SpFi for predicting mortality

The dataset for the evaluation of ML algorithms (Table 3 and Table 4 combined) contained 8587 patients, 6354 (74%) of whom died during the ICU stay and 2233 (26%) of whom survived.

Those 8587 patients were randomly split into the training set (6011, 70%) and the test set (2576, 30%).

Before oversampling, the dataset was imbalanced, containing 4447 patients who died and 1563 who survived.

After oversampling with SMOTE, we obtained a balanced dataset that contained 4447 patients who died and 4447 who survived.

Once we evaluated the model on both PaFi and SpFi datasets (Table 3 and Table 4) using the different machine learning algorithms for classification, we obtained the results shown in Table 5:

- The AUC for the logistic regression is 0.66 in the PaFi dataset and 0.67 in the SpFi dataset.
- The AUC for the random forest is 0.62 in the PaFi dataset and 0.64 in the SpFi dataset.
- The AUC for the XGBoost is 0.65 in the PaFi dataset and 0.66 in the SpFi dataset.
- SVC yields the highest performance with an AUC of 0.67 in the PaFi dataset and an AUC of 0.68 in the SpFi dataset.
- The AUC for the Adaptive Boosting is 0.66 in the PaFi dataset and 0.67 in the SpFi dataset.
- The AUC for the KNN is 0.60 in both PaFi and SpFi datasets.

Table 5. Performance metric for the machine learning algorithms in both datasets: AUC.

	SOFA PaFi on subset srpafi4%>0*	**SOFA SpFi on subset srpafi4%>0***
Model	**AUC**	**AUC**
Logistic Regression	0.66	0.67
Random Forest	0.62	0.64
KNN	0.60	0.60
SVC	0.67	0.68
XGBC	0.65	0.66
AdaBoost	0.66	0.67

* SOFA based on PaFi on subset where patients had SOFA PaFi of 4 and showed differences between the new SOFA SpFi and the gold standard SOFA PaFi.

* SOFA based on SpFi on subset where patients had SOFA PaFi of 4 and showed differences between the new SOFA SpFi and the gold standard SOFA PaFi.

Bar plots shown in Fig. 7 show both PaFi and SpFi AUC values for each of the ML algorithms for classification used.

We observe that the AUC by logistic regression, random forest, SVC, XGBoost, and AdaBoost is higher in the SpFi dataset, meaning that SpFi performed slightly better than PaFi when predicting mortality.

Finally, there are no differences in the AUC by KNN in both datasets, meaning that both PaFi and SpFi performed the same way when predicting mortality.

In summary, we can say that even in patients that showed differences between the new SOFA based on SpFi and the gold standard SOFA based on PaFi there is almost no difference in predicting mortality using PaFi or SpFi methods as both perform similarly. Therefore, SpFi could be used to predict mortality and assess lung failure in a similar way to PaFi. Moreover, the SpFi method could act as a surrogate for the gold standard method due to the advantage that it is a non-invasive method at a high sampling rate.

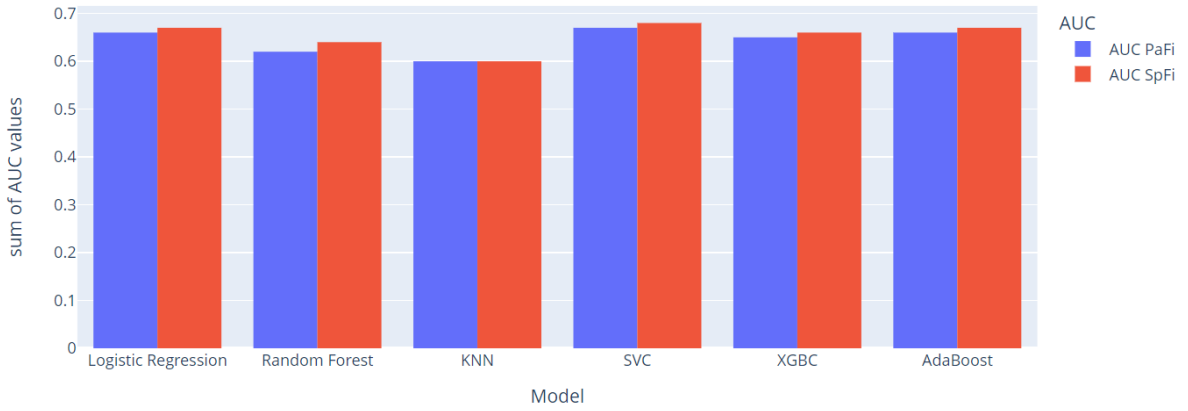

Figure 7. Comparison of PaFi and SpFi AUCs obtained by the several ML algorithms for classification.

4.7 Limitations of the study

Nevertheless, our study has some limitations. First, the development of the new score has been carried out considering patients admitted to a tertiary academic medical center in Boston, MA, USA. Therefore, our score may not perform adequately in other countries or other populations outside the ICU scope.

Another limitation is that it is very difficult to assign lung damage through something different than mortality because lung damage is assessed through PaFi and SpFi ratios. Therefore, we cannot calculate a lung damage label based on the data we already have because we are precisely trying to assign this. What we observe is that although the respiratory SOFA score by itself may not work well for predicting mortality, our new SpO_2-based approach and the gold standard method are interchangeable. Nevertheless, this issue does not infringe on the purpose of our study, which entails developing a non-invasive and high sampling rate surrogate for the current respiratory SOFA score, rather than developing a new score for predicting mortality.

5 Conclusions

This research aimed to develop a SpO_2-based approach to non-invasively assess lung failure at a high sampling rate in order to surrogate the current gold standard, the respiratory SOFA score, an invasive method at a low sampling rate.

By using real-world data from the freely accessible critical care database (MIMIC-IV), applying data transformation techniques, and working with several machine learning algorithms, we accomplished our main goal: developing a non-invasive, automated methodology for monitoring lung damage at a high sampling rate.

We also wanted to characterize the relationship between the SpO_2/FiO_2 ratio and the PaO_2/FiO_2 ratio. The results indicated there is a good or moderate correlation between both ratios.

Furthermore, we evaluated the performance of the new score against the gold standard using a battery of ML classification algorithms (including logistic regression, random forest, k-Nearest Neighbors, Support Vector Classifier, and boosting algorithms) to predict mortality. The new approach performed in a similar way when it came to predicting mortality.

Based on these conclusions, the SpO_2/FiO_2 ratio could be a suitable surrogate for the PaO_2/FiO_2 ratio to non-invasively assess lung failure at a high sampling rate.

However, further research is needed to determine whether this new method could be established as a proper substitute for the gold standard.

6 Further work

Finally, further studies are needed to extend the analysis and confirm the clear benefits of using the new approach instead of the gold standard. In relevance to the first limitation presented in the fourth chapter, an interesting line of research would be to apply this new score to datasets from ICUs other than BIDMC, either in the US or other countries, and evaluate its performance.

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8 Appendices

8.1 Appendix 1. Source code

The source code developed for this project is available on the GitHub repository: https://github.com/bernatsort/Degree_Final_Project.git

8.2 Appendix 2. CITI Program Completion Report

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 1 OF 2
COURSEWORK REQUIREMENTS*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Bernat Sort (ID: 10681494)
- **Institution Affiliation:** Massachusetts Institute of Technology Affiliates (ID: 1912)
- **Institution Email:** bernatsr14@gmail.com
- **Institution Unit:** Intensive Care Unit
- **Phone:** 977 29 58 00

- **Curriculum Group:** Human Research
- **Course Learner Group:** Data or Specimens Only Research
- **Stage:** Stage 1 - Basic Course

- **Record ID:** 45943894
- **Completion Date:** 09-Nov-2021
- **Expiration Date:** 08-Nov-2024
- **Minimum Passing:** 90
- **Reported Score*:** 100

REQUIRED AND ELECTIVE MODULES ONLY	DATE COMPLETED	SCORE
Belmont Report and Its Principles (ID: 1127)	08-Nov-2021	3/3 (100%)
History and Ethics of Human Subjects Research (ID: 498)	08-Nov-2021	5/5 (100%)
Basic Institutional Review Board (IRB) Regulations and Review Process (ID: 2)	08-Nov-2021	5/5 (100%)
Records-Based Research (ID: 5)	08-Nov-2021	3/3 (100%)
Genetic Research in Human Populations (ID: 6)	09-Nov-2021	5/5 (100%)
Populations in Research Requiring Additional Considerations and/or Protections (ID: 16680)	09-Nov-2021	5/5 (100%)
Research and HIPAA Privacy Protections (ID: 14)	09-Nov-2021	5/5 (100%)
Conflicts of Interest in Human Subjects Research (ID: 17464)	09-Nov-2021	5/5 (100%)
Massachusetts Institute of Technology (ID: 1290)	09-Nov-2021	No Quiz

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

Verify at: www.citiprogram.org/verify/?k35e747f1-f337-42c1-9cf7-50d3814e4da6-45943894

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COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 2 OF 2
COURSEWORK TRANSCRIPT**

** NOTE: Scores on this Transcript Report reflect the most current quiz completions, including quizzes on optional (supplemental) elements of the course. See list below for details. See separate Requirements Report for the reported scores at the time all requirements for the course were met.

- **Name:** Bernat Sort (ID: 10681494)
- **Institution Affiliation:** Massachusetts Institute of Technology Affiliates (ID: 1912)
- **Institution Email:** bernatsr14@gmail.com
- **Institution Unit:** Intensive Care Unit
- **Phone:** 977 29 58 00

- **Curriculum Group:** Human Research
- **Course Learner Group:** Data or Specimens Only Research
- **Stage:** Stage 1 - Basic Course

- **Record ID:** 45943894
- **Report Date:** 09-Nov-2021
- **Current Score**:** 100

REQUIRED, ELECTIVE, AND SUPPLEMENTAL MODULES	MOST RECENT	SCORE
Basic Institutional Review Board (IRB) Regulations and Review Process (ID: 2)	08-Nov-2021	5/5 (100%)
Belmont Report and Its Principles (ID: 1127)	08-Nov-2021	3/3 (100%)
Records-Based Research (ID: 5)	08-Nov-2021	3/3 (100%)
Genetic Research in Human Populations (ID: 6)	09-Nov-2021	5/5 (100%)
Research and HIPAA Privacy Protections (ID: 14)	09-Nov-2021	5/5 (100%)
History and Ethics of Human Subjects Research (ID: 498)	08-Nov-2021	5/5 (100%)
Populations in Research Requiring Additional Considerations and/or Protections (ID: 16680)	09-Nov-2021	5/5 (100%)
Conflicts of Interest in Human Subjects Research (ID: 17464)	09-Nov-2021	5/5 (100%)
Massachusetts Institute of Technology (ID: 1290)	09-Nov-2021	No Quiz

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

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