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SpO_2/FiO_2 Ratio (SF Ratio) As a Predictor of Mortality in ICU Patients: Retrospective Study Using MIMIC III Database.

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Capstone Final Report for BSc (Honours) in

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Contents

Chapter 1

Clinical Background

1.1 Importance of Biomarkers in ICU Studies

Allocation of resources to patients to minimize mortality is a constant priority for healthcare professionals. This is especially important in the area of healthcare we have chosen to focus on in this paper: critical care, where resources such as equipment and attention of specialists are scarce. A critical care specialist focuses on the most vulnerable and urgent patients who are placed in an Intensive Care Unit (ICU). In this setting, the specialist is often faced with a difficult decision of which patients to allocate resources to. An unfortunate reminder that has recently put such a predicament under the spotlight is the COVID-19 global pandemic. A recent study on ICU capacity in Wuhan, the disease's epicentre in China, states that at a point during the current crisis the number of COVID-19 patients who need ICU resources is 1120. However, only 600 ICU beds existed. As a result, only 25% of the patients who had died by the time of the study received the intubation and mechanical ventilation that they required (Wu and McGoogan, 2020). In Lombardy, the disease's epicentre in Italy, a study states that under pre-crisis conditions, the city's total

ICU capacity of 720 already operates at 85% - 90% occupancy during winter months. To make things worse, during the first two weeks after the city's first confirmed COVID-19 case, the number of COVID-19 related ICU admissions rose exponentially to 556. Moreover, the exponential estimate for the total number of COVID-19 ICU admissions in the following two weeks was 14,452 - an even more drastic disparity between supply and demand of ICU resources (Grasselli, Pesenti, and Cecconi, 2020). Hence, ICU capacities are stressed under normal conditions and even further during times of crises. Faced with such a perpetual dilemma of resource allocation, a critical care specialist uses various biomarkers (physiological indicators) in order to try and predict severe outcomes in the patients cohort. As such, a persistent priority in medical research is the discovery and analysis of connections between various biomarkers and unfavourable patient outcomes (Ware, 2017).

1.2 Problem: PF Ratio is an Important but Challenging Biomarker

One such biomarker that is tracked in ICU settings is the PaO_2/FiO_2 ratio (PF ratio). The numerator, PaO_2 refers to the partial pressure of oxygen in arterial blood. It is measured in mmHg via drawing a sample of blood from an artery in the wrist or groin, and analysing it in the laboratory. The denominator, FiO_2 refers to the initial fraction of inspired oxygen and is approximately 21% in breathable atmospheric air. The PF ratio is used to monitor the patient's pulmonary functions. In an ICU, it can be controlled by providing the patient with oxygen concentrations above

21% using devices such as a mechanical ventilator. It is most notably used in the diagnosis of fatal illnesses such as Acute Respiratory Distress Syndrome (ARDS) (Bernard et al., 1994). Moreover, it has been shown to be a significant identifier of mortality risk in the general ICU population (Villar et al., 2011) as well as in specific subsets of patients such as newborns with Meconium Aspiration Syndrome (MAS) (Narayanan et al., 2019) and post-operation cardiac surgery patients (Esteve et al., 2014).

Despite the various merits of the PF ratio in diagnosing patients and maintaining their stability, there is a major challenge associated with its use - the measurement of its numerator, PaO_2 . The procedure is invasive and delayed, making it not feasible to track at frequent intervals for all patients.

1.3 Motivation: Can SF Ratio be an Alternative to PF Ratio and for who?

A biomarker that is more convenient to measure than PaO_2 is SpO_2 or peripheral capillary oxygen saturation. It is defined as the ratio of oxygenated haemoglobin to the total amount of haemoglobin in the blood. It is measured using a pulse oximeter, which uses that oxygenated and deoxygenated haemoglobin absorb and radiate particular wavelengths of light to different extents (Jubran, 1999) . The oximeter illuminates light at specific wavelengths through the skin (usually at the fingertips) and almost instantaneously calculates the ratio of absorption of these wavelengths to extrapolate the proportion of oxygenated haemoglobin in the

blood, or SpO_2 (Jubran, 2015). Therefore, unlike PaO_2 , SpO_2 can be measured in a non-invasive and instantaneous manner.

Using SpO_2 instead of PaO_2 in the calculation of the PF ratio gives a different biomarker ratio - SpO_2/FiO_2 ratio (SF ratio). Although the SF ratio might seem as an intuitive replacement to the PaO_2/FiO_2 ratio , a critical difference between PaO_2 and SpO_2 is that the former is generally a more accurate measure of a patient's oxygenation level; it is measured directly from a main artery while the latter is measured at the end of capillaries.

Nevertheless, several studies have linked SpO_2 to mortality in patients with certain conditions. For instance, the Tromsø study in 2015 concluded that an $SpO_2 \leq 95\%$ is associated with all-cause mortality and mortality caused by pulmonary diseases after adjusting for sex, age, history of smoking, self-reported diseases and respiratory symptoms, BMI, and CRP concentration (Vold et al., 2015). Another study established SpO_2 as a predictor of mortality in patients with systemic sclerosis (Swigris et al., 2009).

Similarly, SF ratio, which includes SpO_2 , is linked to mortality in certain patient populations. For instance, SpO_2/FiO_2 Time-at-Risk (SF-TAR), defined as the total time spent with severe hypoxemia (SF ratio $\leq$ 145), is significantly correlated with hospital mortality for mechanically ventilated patients, and is as good or a better predictor of it than arterial gas-derived measurements of the PF ratio. Moreover, SF ratio is a non-invasive surrogate for the PF ratio to diagnose certain patient populations such as children with ALI or ARDS (Rice et al., 2007) and children with smoke inhalation injury (Cambiaso-Daniel et al., 2017).

Hence, on the one hand, both SF ratio and SpO_2 have been shown to be significant predictors of mortality in specific conditions. On the other hand, not all patient subpopulation exhibit a significant link between SpO_2 or SF ratio and mortality. For example, a prospectively planned meta-analysis study using participant data from 5 randomized clinical trials (conducted from 2005-2014) of infants born before 28 weeks' gestation period found no significant difference between a lower SpO_2 target range (85%-89%) and a higher SpO_2 target range (91%-95%) on mortality or major disability at a corrected age of 18 to 24 months (Askie et al., 2018). Therefore, it seems that the use of SpO_2 as a predictor of mortality might not be applicable to all patient phenotypes, with potential for further sub-phenotyping. Such differences between the subpopulation might also be expected for the SF ratio which includes SpO_2 in the numerator.

1.4 Research Statement

The main goal of this capstone can be summarized as follows:
Investigate whether SpO_2/FiO_2 ratio is a predictor of mortality in general ICU patient population, over what range, and for which subsets of the population using a retrospective analysis of ICU patient records.

By focusing on SpO_2/FiO_2 ratio instead of only SpO_2 , we also investigate whether the former is a more helpful predictor as it allows us to account for the different levels of mechanical ventilation that an ICU patient receives. In essence, we believe allows us to account for the patient's ability to convert inspired oxygen to peripheral oxygen saturation at the tissue level.

Chapter 2

Data

2.1 Data Overview

For this capstone we used **MIMIC III**, an openly available relational database developed by the MIT Lab for Computational Physiology. It contains de-identified data of 61,532 intensive care unit stays: 53,432 stays for adult patients and 8,100 for neonatal patients at the Beth Israel Deaconess Medical Center over the June 2001 - October 2012. It includes demographics, vital signs, laboratory tests, medications, mortality, etc. The database is divided into different tables of data that contain information about a patient's stay and are linked to each via identifiers such as a unique hospital admission ID and a unique patient ID.

2.2 Data Extraction

For the patient and stay identifiers we extract SUBJECT_ID, HADM_ID from `ADMISSIONS` table and ICUSTAY_ID from `ICUSTAYS` table. From the `ADMISSIONS` table we extract the time of death of the patient if applicable and if it lies between the ICU admission time and ICU discharge time in

ICUSTAYS table we indicate ICU mortality. Similarly if the time of death is between admission time and discharge time in the ADMISSIONS table, we indicate Hospital mortality. From the Patients table we extract the gender of the patients' and calculate their age.

For all patients and ICU stays we extract the FiO_2 values and their chart times from the CHARTEVENTS table. Keeping in mind that at normal atmospheric conditions, FiO_2 is around 21%, we apply the following transformations. For the values between 0 and 1, we convert them to percentages by multiplying by a 100 and only keep those between 21% and 100%. Next, if the reading is recorded as greater than 1 but lower than 21, the value is likely to be erroneous and we discard it. Next, if the value is between 21 and 100, the value is likely to already be a percentage and we take it as such. Finally, we discard all the values above a 100 that are remaining. From the same CHARTEVENTS table we extract the patients' height and weight.

From the CHARTEVENTS table, we also extract SpO_2 values and chart times but we only keep those which indicate 0 for ERROR which stands for error in measurement. Moreover, we filter the values and we discard those below 10 and above a 100 since they are either physiologically impossible or unlikely.

At the end of this stage, the current dataset accounts for 46,476 Patients, 61,532 ICU Stays with 12,713,362 observations of either SpO_2 or FiO_2 or both. On further examination of the data, we find that for every FiO_2 measurement for a given ICU stay, for a given unique patient, there is a corresponding SpO_2 measurement at the same chart time but not vice versa. Accordingly, we restrict my data to only those chart times

with both SpO_2 and FiO_2 measurements. This further subsets the number of observations further into 703,201 observations.h

Chapter 3

Methods: How to model effect of Biomarkers on ICU mortality?

3.1 Analysis Goal

To reiterate our goal, we not only want to test the significance of the correlation between SF ratio and patient outcome , we also, perhaps more importantly, want to examine over what ranges of SF ratio does significance hold if present. Moreover, if we do find a significant correlation, we want to examine whether such a relationship between SF ratio and patient outcome holds for various subsets of the population. Therefore, we need to find a method of modelling that allows us to examine for more than mere significance of the biomarker.

3.2 The Problem with Generalized Linear Models: They're Linear

When we think of binary response variables such as mortality, we intuitively think of a linear logistic regression. The linear logistic regression

model belongs to a family of models called Generalized Linear Models (GLM). The word 'Linear' in the name does not stand for the relationship between the response variable and the predictor being a straight line, but rather to the fact that the predictor or a function of is is a modelled by a **linear** combination of the covariates. The general form of a GLM with m covariates is:

$$g[\mathrm{E}(Y)] = \beta_0 + \beta_1 x_1 + \ldots + \beta_m x_m$$

where g is called the link function linking the expected value of Y with a linear combination of the covariates, $\beta_0 + \beta_1 x_1 + \ldots + \beta_m x_m$ (Wood, 2017). That is, the model only allows for the response variable to be connected to the covariates in a linear manner. Since our goal is to explore an unknown relationship between mortality and SF ratio, we cannot introduce bias into our modelling by assuming this linear relationship.

3.3 General Additive Models

3.4 G-Computation

Chapter 4

Covariates

4.1 Covariate Selection

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4.1.1 To Ratio or not to Ratio

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4.1.2 Does Transformation help?

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4.2 Timeframe of SF Ratio aggregation

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Chapter 5

Analysis and Findings

5.1 Logistic Regression

I first compute the average SF ratio per ICU stay. Next, I fit the following logistic regression :

$$\ln\left(\frac{M}{1-M}\right) = \beta_0 + \beta_1(\text{Average SF Ratio}) + \beta_2(\text{Gender}) + \beta_3(\text{Age}) + \beta_4(\text{BMI}) + \beta_5(\text{Sofa}$$

where M is Hospital Mortality, BMI is the Body Mass Index of the patient and Sofa Total Score is a . The results are as follows:

Feature	**Estimate**	**Std. Error**	**z-value**	**p-value**
Intercept	-0.3427213	0.2362569	-1.451	0.147
Average SF Ratio	-0.0097838	0.0008024	-12.193	<2e-16
Gender (M)	-0.3579267	0.0585947	-6.109	1.01e-09
Age	0.0045151	0.0005280	8.551	<2e-16
BMI	-0.0316707	0.0044837	-7.063	1.62e-12
Sofa Total Score	0.1964941	0.0083214	23.613	<2e-16

TABLE 5.1: Results of Logistic Regression

Hence, the Average SF ratio is significantly correlated with Hospital

Mortality and a unit increase in SF ratio decreases odds of hospital mortality by 1.19%.

5.2 Generalized Additive Model

A logistic regression assumes a linear relationship between mortality and the different features which may not necessarily be true. To explore a potential non-linear relationship I use a generalised additive model. A generalized additive model is an extension of a generalized linear model with a linear predictor involving a sum of smooth functions of covariates (Hastie, 2017). The general model can be expressed as follows (Wood, 2017):

$$g(\mu_i) = \mathbf{A}_i\boldsymbol{\theta} + f_1(x_{1i}) + f_2(x_{2i}) + f_3(x_{3i}, x_{4i}) + \ldots$$

where $Y_i \sim \text{EF}(\mu_i, \phi)$, Y_i is the response variable, $\mu_i \equiv \mathbb{E}(Y_i)$ and $\text{EF}(\mu_i, \phi)$ denotes an exponential distribution with mean μ_i and parameter, ϕ. Also, f_j are smooth functions of the covariates, x_k (Wood, 2017).

Now fitting a GAM model to our data with Hospital Mortality as response variable and a smoothening function applied to predictors Average SF Ratio, Age and Length of ICU Stay and Gender taken as a linear predictor. We obtain the following results:

Feature	**edf**	**Ref.df**	**Chi.sq**	**p-value**
Average SF Ratio	6.968	8.078	957	<2e-16
Age	5.582	6.665	411.2	<2e-16
Length of ICU Stay	5.262	6.268	306.8	<2e-16

TABLE 5.2: Results of GAM

The result of the model in table 5.2 shows that there is a statistically significant correlation between Hospital Mortality and Average SF Ratio. I visualize this relationship below in fig 5.1. The visualizations for all the predictors can be found in Appendix A.

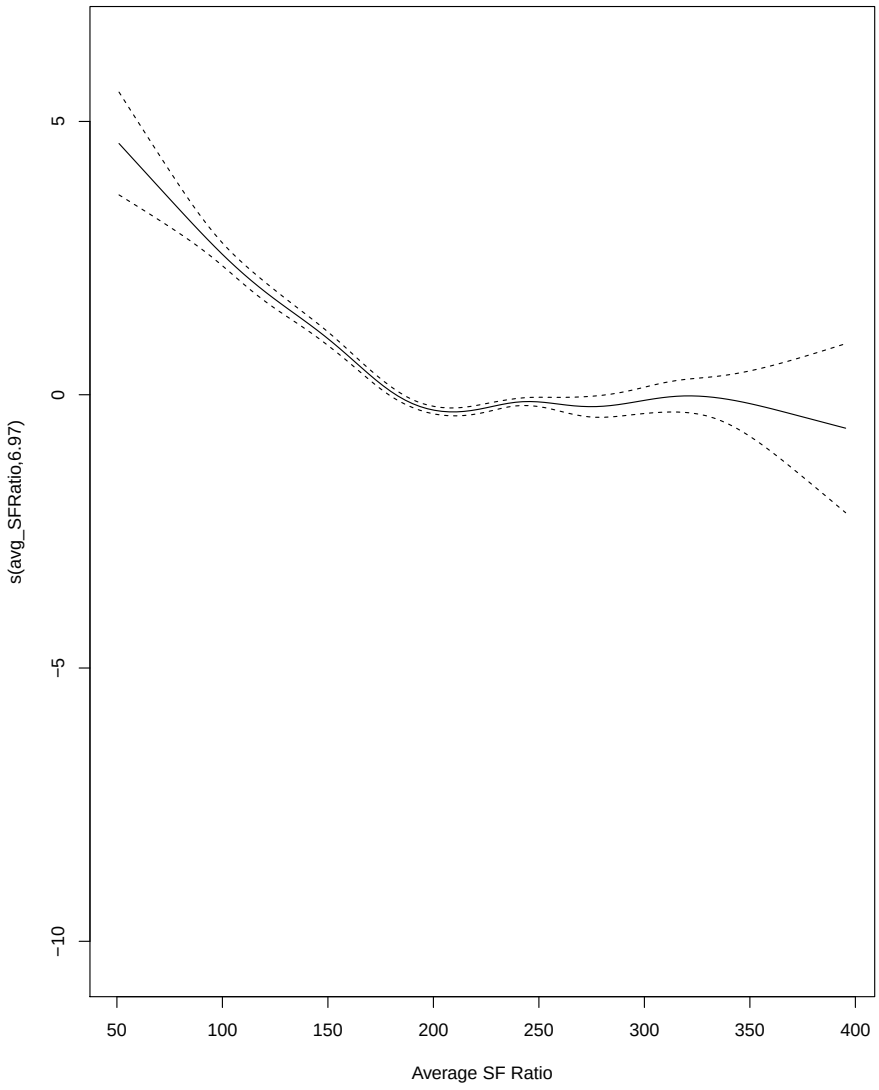

FIGURE 5.1: Results of GAM model for relationship between Average SF Ratio and log odds of Hospital Mortality

From fig 5.1 we see that a increase in Average SF Ratio from around

100 to around 200 causes a reduction in the log odds of Hospital Mortality with minimal standard error.

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Appendix A

Other Figures

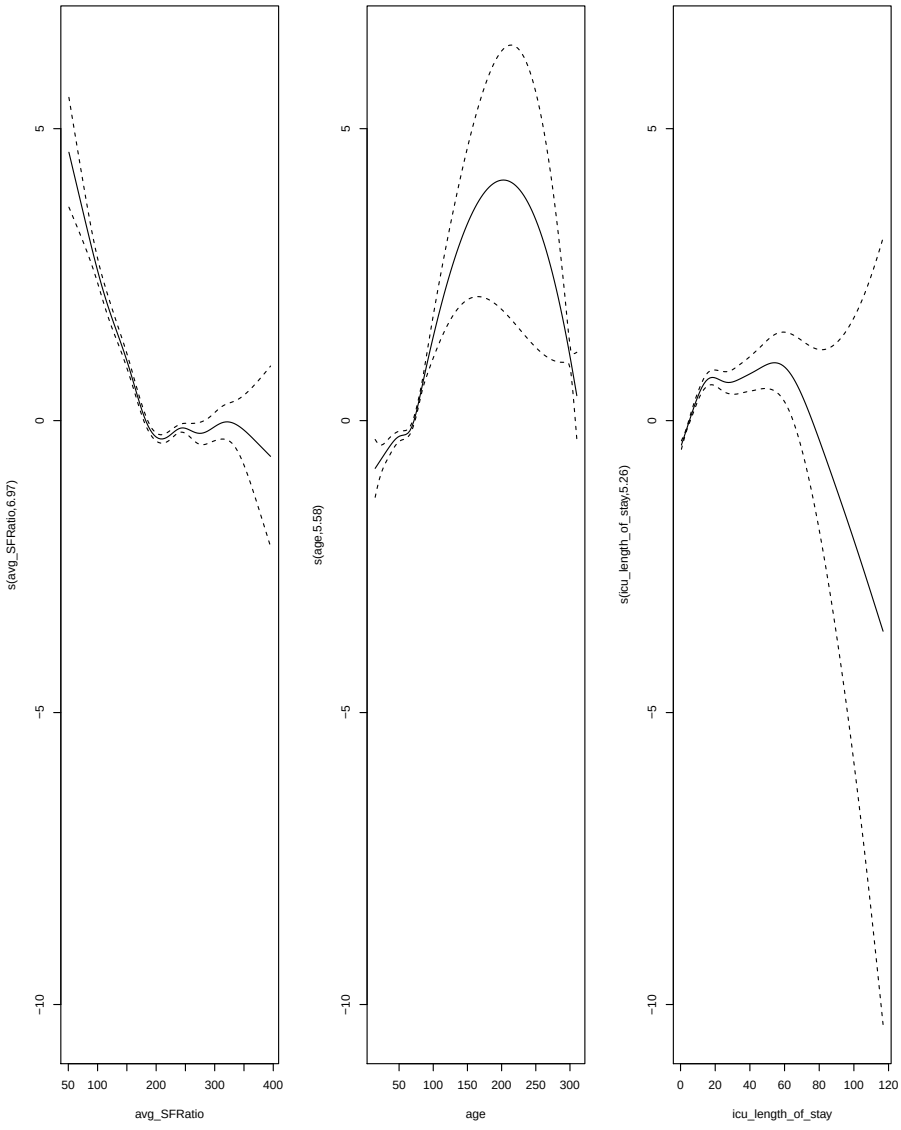

FIGURE A.1: Results of GAM model