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Quantitative Modelling of COVID-19 Severity

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Abstract

Background: Coronavirus Disease 2019 (COVID-19), a new group of RNA viruses that appeared in Wuhan in the Republic of China in December 2019 and declared a pandemic by the World Health Organization (WHO) in March 2020. Since its emergence, it has been linked to a number of physiological factors that can help predict the severity of the illness. This study aims to explore some of these factors and their effect on the illness clinical course.

Materials and methods: This is a retrospective cross-sectional study of 416 COVID positive patients, aged between 5 months and 92 years, who were admitted to COVID facilities of the Ministry of Health of the Kingdom of Bahrain, over the period April to August 2020. Physiological factors that were studied among those patients included both vital signs and laboratory values.

Results and discussion: The study established a correlation between patients' hemoglobin levels and their ages, pulse rates and blood pressure readings, with age being the highest influencing factor. Henceforth, a Generalized Linear Model (GLM) was established to predict patients' hemoglobin level and thereafter the severity of their illnesses. The correlation between actual and predicted patient hemoglobin levels were found to be statistically significant with a P value of <0.05.

Conclusion: With many factors contributing to the clinical course of COVID disease, establishing a model to predict one of those factors, such as patients' hemoglobin levels as in the index study, is critical for the understanding of the disease and hence, establishing better disease outcomes.

Keywords: Infection; COVID; Virus

Introduction

In December 2019, the province of Wuhan, China reported the emergence of clusters of pneumonia cases that were later linked to the b-coronavirus. Coronaviruses are RNA positive viruses that are subdivided into four main genera; α, β, γ, σ-Cov. The former two can infect mammals and are responsible for about 10%-30% of the mild common cold. Of interest, two forms of β-coronavirus, known as Severe Acute Respiratory Syndrome SARS-CoV and Middle Eastern Respiratory Syndrome MERS-CoV, accounted for the past two severe and fatal outbreaks witnessed in 2002 and 2012, respectively [1].

Since its emergence in China, COVID-19 has spread globally with over 3,513,328 infected cases and 245,540 deaths documented worldwide. The first case in Bahrain was reported on February 21st, 2020. As of Oct 9th, 2020, the total number of active cases in Bahrain has reached 4,304 with a total of 264 deaths [2].

Since its outbreak, the core symptoms of COVID-19 have been reported to commonly accompany symptoms of fever, cough and shortness of breath [3].

Investigations convey that older male patients with co-existing chronic comorbidities were more susceptible to contracting the disease, in addition to developing a more severe course [4]. Hypertension was found to be the most prevalent comorbidity among deaths of COVID-19; one study shows [5]. The same case series also concluded that delayed initiation of mechanical ventilation was common among non-survivals [5]. Another research demonstrates that old age, elevated SOFA scores and d-dimer levels are associated with worse disease outcomes. Collectively, common findings amongst intensive care admissions were age, chronic comorbidities, low WBC count, high alanine aminotransferase, creatinine kinase, d-dimer, prothrombin time and troponin [6].

The current diagnosis of COVID-19 includes a PCR test that identifies if a patient is positive or negative of the virus. Yet, PCR results do not necessarily reflect infection severity. Along with the PCR test, care providers also collect vital signs (including pulse, systolic blood pressure and temperature) along with pre-therapy lab tests (including Bilirubin, Platelets, Creatinine, Troponin, D-dimer, WBC and Hemoglobin Level). Vital signs are then collected again post-therapy. Despite the affluence of such data, precise prediction of COVID-19 severity is still limited, while its correlation with asymptomatic patient vital signs is unclear.

Given the above mentioned limitations, there exists a need in the art for a quantitative approach that provides a better understanding of COVID-19 associated physiological factors. Thus, this study will develop a statistical model that predicts COVID-19 severity, by exploring COVID-19 associated physiological factors.

Materials and Methods

Study design

Retrospective analysis of cross-sectional data of patients admitted to the facilities in the Ministry of Health, Kingdom of Bahrain between April and August 2020. Admission to Ministry of Health facilities was

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mainly from the population screening for COVID-19, which included mobile fever clinics. According to the local protocols the diagnostic test used for SARS-CoV-2 was real-time RT-PCR: All were tested for E gene and positive samples were confirmed after being tested for N gene and RdRp gene (from Tib Molbiol). Viral clearance was defined as two RT-PCR-negative tests 24h apart.

Ethical considerations

The study was approved by the national COVID-19 research ethics committee, Kingdom of Bahrain.

Data collection

Data were extracted using specially designed forms to standardize data collection. Variables of interest were:

Socio-demographic and anthropometric measurements (age, gender, comorbidities, etc.),

Symptomatology (temperature, pulse, etc.),

Managements (medications, oxygen therapy, etc.),

Outcome of the disease (treatment outcome, survival).

Statistical analysis

Statistical analysis was performed using the MATLAB statistical computer package. Statistical modelling was achieved using multiple regression and General Linear Model (GLM) analysis. Pearson correlation coefficient was used to model associations between COVID-19 and selected variables.

Assumptions for regression analysis were checked before performing the analytics.

Statistical significance was set at P 0.05.

Investigated population exploration

The investigated data were of 416 COVID-19 positive patients aged between 5 months-92 years with a mean of 46.75 years, a median of 47 years and a range of 98.83 (Figure 1). Females composed 57.5% of this specific data set. Contrary to some current investigations, 74.22% of the investigated patients had zero comorbidities (Figure 2). The most dominant comorbidity was diabetes followed by hypertension. Similarly, only one patient was found to suffer from immunosuppressive factors.

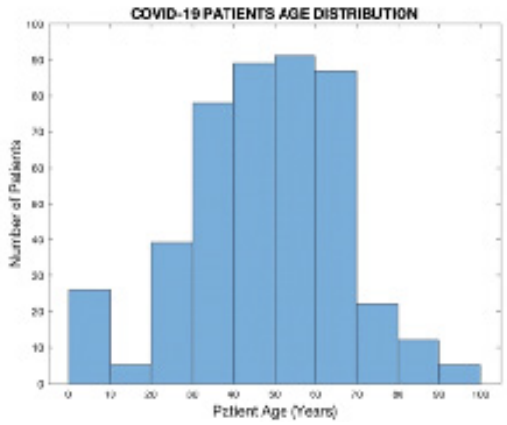

Figure 1: Population age distribution.

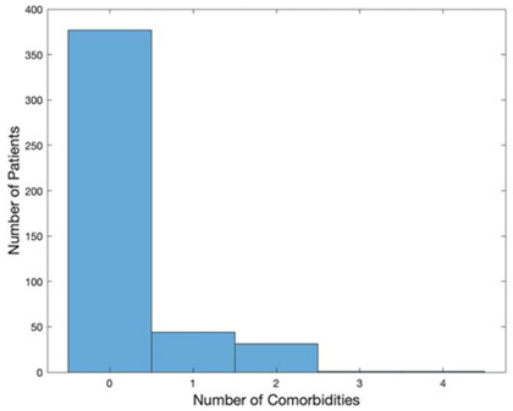

Figure 2: Number of comorbidities distribution amongst COVID-19 patients.

Physiological measurements exploration

Investigated physiological measurements in this study were categorized as initial assessment vital signs (temperature, systolic blood pressure, pulse) or pre-therapy lab tests (Bilirubin, Platelets, Creatinine levels, WBC, Hemoglobin levels) (Figures 3a-3e).

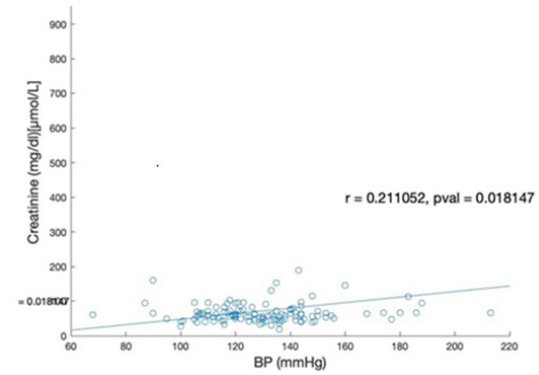

Figure 3a: Correlation between BP (mmHG) and creatinine (mg/dl)[µmol/L].

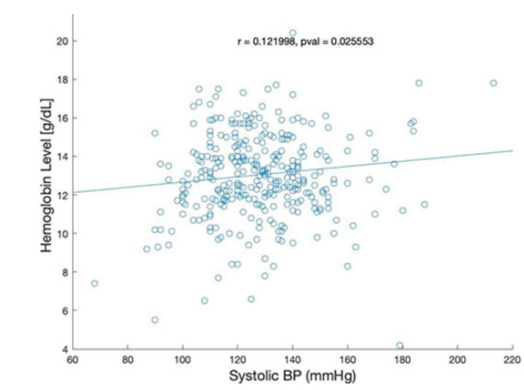

Figure 3b: Correlation between systolic BP (mmHg) and Hemoglobin level[g/dL].

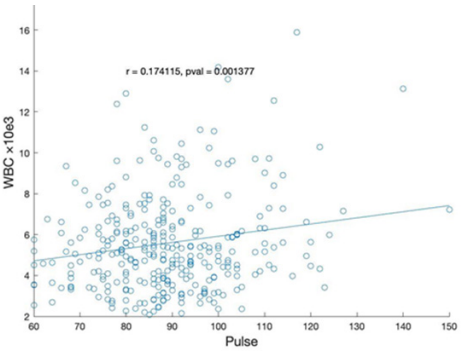

Figure 3c: Correlation between pulse and WBC ×10e3.

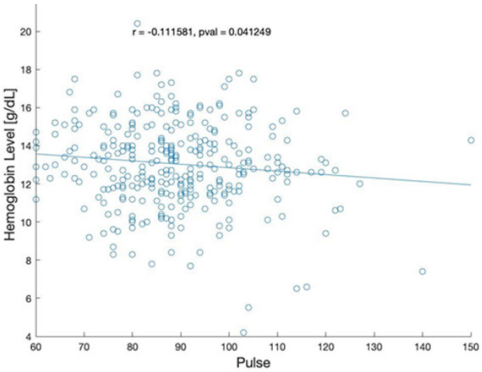

Figure 3d: Correlation between pulse and haemoglobin level [g/dL].

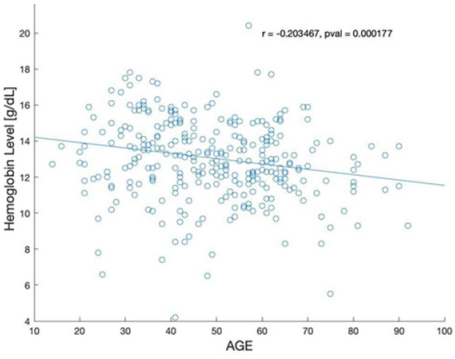

Figure 3e: Correlation between age and haemoglobin level [g/dL].

The investigated population had a mean temperature of 36.98°C, a mean pulse of 89.88 and a mean BP of 127.95 mmHg. According to clinical standards, each of the mean temperature, pulse and systolic BP falls within the normal physiological ranges for healthy patients, as established by previous investigations [7-9]. These results highlight the challenge of being able to identify COVID-19 positive patients using only patient physiological measurements.

Bilirubin level was found to have a mean of 10.16 µmol/L, Platelets were at a mean of 238.29 (x10e3/ml) and lastly, Creatinine levels were at a mean of 75.32 µmol/L, all of which are translated into a 0 SOFA score [10]. Mean hemoglobin level was 12.95 g/dL whilst mean WBC is 128.81 × 10^3.

Results

Univariate analysis was executed to highlight the correlation between vital sign parameters and pre-therapy lab tests. Systolic blood pressure was found to correlate significantly with each of the creatinine and hemoglobin levels, whilst pulse correlated with each of WBC and hemoglobin levels. Interestingly, a significant c orrelation w as a lso established between each of the age and hemoglobin levels.

Discussion

Hemoglobin levels can be physiologically marked by each pulse and blood pressure. Interestingly, patient age has the highest correlation value with hemoglobin levels. All of these correlations have already been established by previous investigations, yet, in populations other than COVID-19 patients [11].

Similarly, blood pressure can be considered as a marker for creatinine, whilst pulse would map onto WBC [12]. These observations were also established in previous investigations, implying that COVID-19 patients exhibit similar physiology to that of healthy individuals or who suffer from other disorders.

GLM model design

According to the abovementioned results, Hemoglobin correlated with three parameters including age, pulse and systolic blood pressure. Hemoglobin levels were also found to be reduced in COVID-19 patients [13].

Accordingly, in this study we will develop a Generalized Linear Model (GLM) using patient age, pulse and blood pressure as inputs, to predict hemoglobin levels, thus COVID-19 severity, as an output (Figure 4). The model was trained on 80% of the population and tested on the remaining 20%.

Individuals were randomly selected in either set were randomly selected.

GLM model results

GLM model weights were highest for Age and lowest for systolic blood pressure (Figure 5). The coefficient distribution in this specific model implies that age has the greatest impact on predicted COVID-19 patient hemoglobin level, whereas systolic blood pressure is the least influential. The correlation between actual and predicted patient hemoglobin levels were found to be 0.311 ($P<0.05$) in the training set and 0.2633 ($P<0.05$) in the testing set. The average prediction error was 13.5% and 12.147% in the training and the testing set respectively (Figure 6).

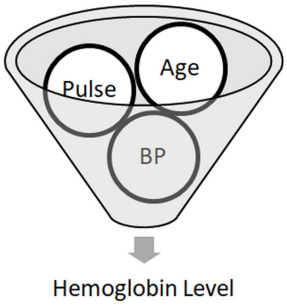

Figure 4: Predict haemoglobin levels using patient physiological parameters and demographics.

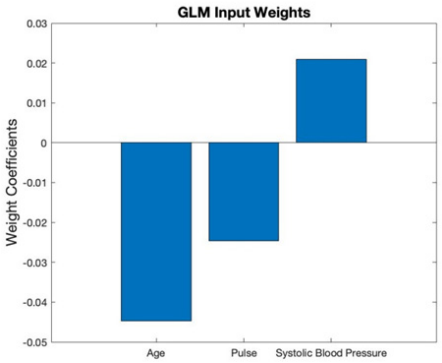

Figure 5: GLM model input weights.

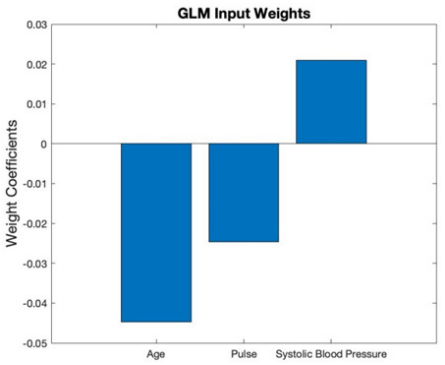

Figure 6: GLM model correlation between the actual and the predicted haemoglobin levels for both the training and the testing groups.

Future directions

In the future analysis, it would be worthwhile to add in the investigated population COVID-19 patients who exhibit severe symptoms. We predict that training the model on these patients would improve the model prediction accuracy.

It would also be interesting if future analysis includes other lab tests that were proven to be indicative of COVID-19 severity and to assess the possibility of incorporating them in a holistic predictive model [14].

Conclusion

Despite the affluence of data collected from COVID-19 patients, precise prediction of infection severity based on initial assessments is limited. In this investigation, we develop a model that predicts COVID-19 patients' hemoglobin levels using each the patient's age, pulse and systolic blood pressure. According to earlier findings, the predicted hemoglobin levels from the model are to indicate COVID-19 severity. Model prediction was significantly consistent in each of the training and the testing sets with a prediction error of 13.5% and 12.147% in both the testing and training sets respectively. This investigation has also highlighted blood pressure and pulse as biomarkers for each of the pre-therapy creatinine levels and WBC.

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