D-Dimer Elevation Matters to Predict COVID-19 Severity: A Machine Learning Approach

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***Abstract*—Although previous studies using limited data have documented an association of D-dimer levels with COVID-19 severity, the role of D-dimer in the progression of COVID-19 remains unclear and requires further investigation using data from larger cohorts. We used traditional statistical modeling and machine learning methods to examine critical factors influencing the D-dimer elevation and to characterize associated risk factors of D-dimer elevation over the course of inpatient admission. We identified 20 important features to predict D-dimer levels, some of which could be used to predict and prevent the D-dimer elevation. Laboratory monitoring of D-dimer level and its risk factors at early stage can mitigate severe or death cases in COVID-19.**

***Keywords*—COVID-19, D-dimer, machine learning, risk factor analysis**

I. Introduction

COVID-19 has affected over 500.1 million population worldwide and resulted in approximately 6.1 million deaths as of April 15, 2022, since the global outbreak in December 2019 [1]. For the critically ill and death cases of COVID-19, there is an increased risk of hypercoagulability and venous thromboembolism (VTE) events, leading to severe thrombo-inflammation [2] conditions, where D-dimer level elevates [3]. This study aims to explore the risk factors of elevated D-dimer levels for predicting the disease severity of COVID-19 based on a set of clinical data of hospitalized patients.

II. Research Questions

Previous studies have reported higher D-dimer levels in severe COVID-19 cases [4] [5] [6] [7] and D-dimer $\geq$ 2.0 μg/mL at admission was used to predict in-hospital mortality in COVID-19 patients [8] [9] [10] [11] [12]. D-dimer elevation was found to be associated with patient demographics, comorbidities, lab results, and overall higher incidence of critical illness [8] [9] [11] [13]. However, due to small sample sizes, limited data on essential covariates, and the absence of standardization of the admission laboratory protocol, the role of D-dimer in the progression of COVID-19 has not been fully investigated. Our study is crucial to analyzing the possible predictive characteristics of D-dimer elevation in a large COVID-19 inpatient cohort and identifying risk factors associated with high D-dimer levels. We used statistical modeling and machine learning methods in this study. Our primary research questions (RQ) are as follows:

RQ1: What is the relationship of high D-dimer level and related predictors leading to disease severity of COVID-19?
RQ2: What is the role of patients' pre-existing comorbidities and lifestyle behaviors in detecting high D-dimer levels?

III. Study Design

A. Data

Our sample consisted of 1005 COVID-19 inpatients admitted to a large US hospital 03/2020 to 07/2020, using detailed data on various clinical and biochemical laboratory test results at admission and throughout the course of hospital stay.

B. Methodology

The study target is a high D-dimer level (y/n) using a cutoff at 2.0 μg/mL; and we used patients' demographics, clinical outcomes, lab results, and medication records as predictors.

We utilized multiple analytic methods including a) descriptive statistics using chi-square tests at baseline, b) adjusted multivariable regression modeling, and c) evaluation of feature importance using two decision-tree-based supervised machine learning algorithms, i.e., random forest and XGBoost methods.

C. Primary Findings

Of a total of 1005 COVID-19 inpatients, 545 who had at least one D-dimer record, were included in the study in which 120 patients were tested with elevated D-dimer levels. After cross-comparing the results using random forest and XGBoost models, we found the most influential features to predict the elevated D-dimer were age, weight, body mass index (BMI), the highest body temperature, Cheyne-Stokes respiration (CSR), lactate dehydrogenase (LDH), ferritin (FER), history of Diabetes, and Ceftriaxone use (antibiotic).

D. Expected Results

Conducting continual laboratory monitoring of the D-dimer level to evaluate COVID-19 infection and using identified critical risk factors from early stage may enable clinicians to triage patients into risk levels, initiate appropriate therapeutic strategies, and tailor care management to each patient to minimize the morbidity and mortality of COVID-19.

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