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Importance of Handgrip Strength and Endurance Time for Predicting COVID-19 Mortality in Older Adult Patients: K-Nearest Neighbors (K-NN) Algorithm

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ABSTRACT

The study aimed to investigate the role of handgrip strength (HGS) and muscular endurance time (ET), as assessment measures for physical frailty and muscle function, in predicting the COVID-19 mortality of elderly patients admitted to the intensive care unit (ICU). This prospective observational cross-sectional study was conducted on 872 COVID-19 patients (415 females and 457 Males) aged 65–90 years admitted to ICU. Demographic data, underlying comorbidities, COVID-19-related symptoms, as well as laboratory and computed tomography (CT) findings were obtained from the patient's medical records. Using a JAMAR® hydraulic dynamometer, the average HGS (kg) after three measurements on the dominant side was recorded as the outcome for analysis. The threshold of the Low grip strength was defined as less than 26 kg and 14 kg for males and females, respectively. This is based on the consideration that low grip is two standard deviations below the gender-specific peak mean value. Muscular ET was also calculated after an additional trial, in which patients were asked to maintain the grip, and the value was measured in seconds when strength dropped to 50% of its maximum level. Subsequently, all thirty-one features were entered into the k-Nearest Neighbors (k-NN) algorithm to investigate the possible relationship between HGS and ET with COVID-19 mortality in elderly patients admitted to ICU. The results showed that chronic obstructive pulmonary disease (COPD), low grip strength, C-reactive protein (CRP), SaO_2, and ET were found to be the most relevant components for possible COVID-19 mortality prediction, respectively. Further, the k-NN classifier achieved the highest classification accuracy of 95.21% to predict COVID-19 mortality, under the 10-fold data division protocol. Along with the well-known clinical risk factors, HGS and ET can be quick and low-cost prognostic tools in the mortality rate of elderly patients with COVID-19.

Keywords: COVID-19 mortality, Older adults, Muscle strength, Machine learning, Muscular endurance time

INTRODUCTION

The elderly vulnerability and higher risk of morbidity and mortality due to a pre-existing condition leading to infection from the COVID-19 pandemic have been well documented (Zhang et al., 2023; Mattiuzzi and Lippi, 2022). Two meta-analyses by Pijls et al. (2021) and Guan et al. (2020) showed that elderly patients aged $\geq$ 65 years have an approximately 65% higher risk of severe COVID-19 disease and 81% of the total mortality, respectively (Pijls et al., 2021; Guan et al., 2020). Current evidence in elderlies illustrated that an imbalance between catabolic and anabolic processes leads to the activation of the ubiquitin-proteasome system, myocyte apoptosis, and the autophagy-lysosome pathway, and thus reduces muscle protein synthesis and increases muscle degradation in elderly patients (Files et al., 2016; Zhou et al., 2016). The frailty and reduced muscle force-exertion in elderlies with acute and inflammatory lung disease are considered strong reasons for causing malfunction of respiratory muscles, long-term stay in the intensive care unit (ICU), and mortality (Ali and Kunugi, 2021; She et al., 2021).

Handgrip strength (HGS) test is recognized as a non-invasive biomarker in overall body health, physical function, functional recovery, mobility, and mortality (Saremi et al., 2018; Soysal et al., 2021; Soyuer et al., 2022; Malhotra et al., 2020). HGS has also been used to quantify and monitor the effectiveness of various treatment and rehabilitation interventions in patients with cardiovascular and neurological disorders, inflammatory lung diseases, and sarcopenia (Pérez-Mármol et al., 2017). It is well documented that low grip strength (LGS) is associated with age-related loss of muscle mass, disease severity, longer hospital stays, the development of frailty, sarcopenia, and muscle dystrophy (Ali and Kunugi, 2021; Grigioni et al., 2023).

Several input features, strong multicollinearity among explanatory variables affecting disease severity and mortality in COVID-19 patients (i.e. dependent variables), incorrect segmentation, and irrelevant features in studies often made a predictive modeling task more challenging and led to less reliable predictive models. Unlike traditional statistical methods aiming at inferring relationships between variables, Machine Learning (ML) concentrates on making predictions as accurately as possible by using general-purpose learning algorithms (Braga-Neto, 2020). K-Nearest Neighbors (k-NN), as the most popular supervised classifier in ML, can be used to predict which of the independent variables are important on the dependent variables. According to the literature, this type of classifier has effectively been used in previous Computer-Aided Diagnosis (CAD) studies (Polat et al., 2017; Rahman et al., 2020; Mishra and Uyyala, 2021; Shankar et al., 2020; Rostamzadeh et al., 2023). The objectives of the current study were two-fold: (a) investigate the role of handgrip strength and endurance time (ET), as assessment measures for physical frailty and muscle function, in predicting the COVID-19 mortality of elderly patients hospitalized in ICU, and (b) performance assessment of the K-Nearest Neighbors (k-NN) algorithm in predicting COVID-19 mortality of elderly patients.

MATERIAL AND METHODS

Patient Selection

We used electronic medical records to identify all consecutive elderly patients aged 65–90 years who (i) had a laboratory-confirmed SARS-CoV-2 infection (as determined by real-time reverse transcriptase-PCR assays of nasal and pharyngeal swabs), (ii) underwent concomitant systematic variant screening, (iii) none had any fracture/deformity/surgery in upper extremities during the past year, (iv) none had neuromuscular or rheumatic diseases affecting the handgrip strength measurements, and (v) were admitted to ICU between April and September 2021. Also, based on the Asian working group for sarcopenia criteria, patients with appendicular skeletal muscle mass index score <7.0 kg/m^2 were diagnosed as before-COVID-19 sarcopenia and excluded from the study (Vellas et al., 2018). According to World Health Organization (WHO) interim guidance, patients admitted to the ICU had clinical signs of pneumonia (fever, cough, dyspnea, and tachypnea) together with a respiratory rate > 30/min, oxygen saturation (SpO_2) $\leq$ 80%, and extensive lung involvement in CT (CT score > 11) on room air (World Health Organization, 2020). Eventually, 872 COVID-19 elderly patients (415 females and 457 males) aged 65–90 years admitted to ICU were selected. The data were collected and analyzed once all included patients either died or were discharged alive from the ICU.

The study was approved by the Research and Ethics Committees of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHNS.REC.1402.087). Written informed consent was obtained from all participating patients or their immediate family members to obtain permission to use the patient's health records.

Demographic and Clinical Characteristics

Demographic data, smoking status, comorbidities (e.g. hypertension, overweight, diabetes mellitus (DM), hypothyroidism, cardiovascular disease (CVD), bronchial asthma, chronic obstructive pulmonary disease (COPD), and cancer), COVID-19 related symptoms (cough, fever (>37.8 C°), myalgia, dyspnea, anosmia/ageusia, diarrhea, and asymptomatic), and clinical markers values (C-reactive protein (CRP), ferritin, D-dimer, SaO_2, white blood cell (WBC), thrombocyte, lymphocyte, neutrophil, and hemoglobin) were obtained from the medical records of the patients. Participants' stature (cm) and body mass (kg) were measured using the Holtain Harpenden stadiometer (Holtain, Crosswell, UK) and a digital balance (Toledo, Model 2096PP/2, Inc., Brazil), respectively, with light clothing but no shoes. Body mass index (BMI) was calculated as kg/m^2 and classified into three groups: underweight (BMI<18.5), healthy weight (18.5 to 24.9), overweight (25.0 to 29.9), and obese (BMI $\geq$ 30) (Organization, 2000).

Computed Tomography (CT)

The patients' CT scans were obtained in a supine position at the end of inspiration (Valenza et al., 2005), using a GE Brightspeed 16-Slice CT Scanner

(GE Healthcare, Chicago, Illinois, United States). The CT findings were evaluated by a radiologist with 15 years of experience in terms of the presence and patterns of infiltrations as ground-glass opacities (GGO), GGO with consolidation, consolidation, and other (linear opacities, traction bronchiectasis, cysts, and reticular opacities) for each patient's initial chest CT scan and last follow-ups if available (Hansell et al., 2008). The anatomic distribution of the infiltrations was given to the predominant imaging findings in each zone on CT (3 lobes in the right upper, middle, and lower, and 2 lobes in the left upper and lower). Then, we applied a semi-quantitative CT severity scoring system (0 = no anatomic involvement, 1(<5%), 2(5–25%), 3(26–50%), 4(51–75%), and 5(>75%)) for quantifying radiological findings in each lobe (Pan et al., 2020). The total CT score was calculated as the sum of each lobe's scores between 0 to 25.

Handgrip Strength and Muscular Endurance Time

The maximal isometric grip strength was measured (in kg) by the JAMAR® hydraulic dynamometer (Saehan Corporation, Masan-Korea). Before starting the test, hand dominance was determined by asking participants the following question: "Which hand do you write with?". Measurements were made in a sitting posture, with feet on the floor, arms hanging relaxed at the side and neutrally rotated, elbows flexed 90 degrees, and forearm and wrist in a neutral position (0–15 degrees of extension and 0–15 degrees of ulnar deviation) (Richards and Palmiter-Thomas, 1996). The participants performed one repetition in the dominant hand to familiarize themselves with the dynamometer and the test process. The participants were asked to exert their maximal voluntary contraction (MVC) on the dynamometer for 3 seconds. Three MVCs were recorded for each handgrip strength measurement (with a 1-minute rest time between each exertion) and their average value was considered for subsequent analysis. Low grip strength (LGS) was defined as two standard deviations below the gender-specific peak mean value of the healthy adults i.e. <26 kg in males and <14 kg in females (Dodds et al., 2014). To evaluate muscle endurance time (ET), handgrip exhaustion time was calculated after an additional trial, in which patients were asked to maintain the grip, and the value was measured in seconds when strength dropped to 50% of its maximum level (Beaudart et al., 2019).

Descriptive Analysis

Statistical analysis was performed by SPSS 23 (IBM Corporation, New York, NY, United States). The normality test was carried out using the Kolmogorov-Smirnov test for all data sets. Statistical outliers were checked using Grubb's test which is based on the difference between the mean of the sample and the most extreme data considering the standard deviation (Grubbs, 1969). Relative and absolute reliability were assessed for the grip strength and muscle endurance tests using the Intra-class Correlation Coefficient (ICC) and standard error of the measurement (SEM), respectively. Basic descriptive statistics such as means, standard deviation (SD), minimum-maximum, and number (percentage) were calculated for clinical and demographic characteristics as well as chest CT scores. An independent sample t-test was carried out to determine the differences in clinical characteristics between males and females. One-way ANOVA test (with Tukey post-hoc test) and Chi-square or Fisher's exact tests were used to compare the numerical and categorical variables, respectively. The statistical significance was set at $p<0.05$.

In this study, the K-Nearest Neighbors (k-NN) algorithm as one of the most popular supervised classifiers was used to predict which of the demographic factors, clinical symptoms, and biomechanical biomarkers (i.e. independent variables) are important on the COVID-19 mortality (i.e. dependent variable). In this study, we used the filter method to determine the rank of features and select the relevant features by Pearson's correlation coefficient (P) in decreasing order. In the present study, experiments were conducted with the desired value of $k = 10$, and the average results were used to evaluate the model (Karal, 2020; Marcot and Hanea, 2021). The overall machine-learning analysis was programmed using Scikit-Learn 0.20.3, a popular Python ML library (Pedregosa et al., 2011). Sensitivity or recall, specificity, accuracy, precision, F1 score, and area under the curve (AUC) are used to evaluate the classifier's performance. The mathematical formulas to calculate the above performance metrics are shown in equations 1 to 5 (Sokolova et al., 2006; Kumar et al., 2020).

$$\text{Sensitivity or recall} = \frac{TP}{TP + FN} \tag{1}$$

$$\text{Specificity} = \frac{TN}{TN + FP} \tag{2}$$

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \tag{3}$$

$$\text{Precision} = \frac{TP}{TP + FP} \tag{4}$$

$$F1 = \frac{2TP}{2TP + FP + FN} \tag{5}$$

Where, TP: true positive, FP: false positive, FN: false negative, and TN: true negative.

RESULTS

Clinical and Demographic Characteristics

The sample consisted of 872 COVID-19 patients aged between 65 and 90 years old; 457 (52.4%) males and 415 (47.6%) females. The mean age for males and females was 81.1 ± 4.7 and 79.3 ± 5.4 years, respectively. In total, 468 patients died (310 males and 158 females), resulting in a high mortality rate of 53.6% (66.2% and 33.8% for males and females, respectively). Table 1 shows the clinical findings and demographic characteristics of COVID-19 patients according to survived/deceased.

Mean handgrip strength values were lower and the frequency of LGS was higher in the deceased patients vs. the survived group ($p<0.001$). Participants showed high to very high test-retest reliability for the Jamar dynamometer ($0.88 \leq$ ICC ≤ 0.91; P $\leq$ 0.001; n = 50 subjects out of the total sample). Also, mean endurance time values were lower in the deceased patients vs. the survived group for both genders (p<0.001).

Table 1. Clinical biomarkers, medical history, and demographic characteristics of the elderly patients hospitalized in ICU.

Characteristics	Deceased (n = 468)	Survived (n = 404)	p-value
Age (years)	84.2 ± 3.9	72.6 ± 3.9	< 0.001
Gender			
Males	310(66.2%)	139(34.4%)	< 0.001
Females	158(33.8%)	265(65.6%)	< 0.001
B M I (kg/m^2)			
Underweight (<18.5)	17.0 ± 2.8	18.1 ± 3.3	0.768
Health y weight (18.5 to 24.9)	22.6 ± 5.7	22.1 ± 4.2	0.616
Overweight (25.0 to 29.9)	28.8 ± 3.3	25.7 ± 4.7	< 0.001
Smoking, n (%)	156(33.3%)	83(20.5%)	< 0.001
Hospital stay in ICU (day)			
Symptoms at ICU, n (%)	25(7 − 39)	9(6 − 19)	< 0.001
Cough	311(66.4%)	168(41.6%)	< 0.001
Fever (> 37.8C°)	341(72.9%)	159(39.4%)	< 0.001
Myalgia	161(34.4%)	136(33.7%)	0.107
Dyspnea	342(71.1%)	46(11.4%)	< 0.001
Anosmia/ageusia	52(11.1%)	76(18.8%)	0.043
Diarrhea	31(6.6%)	16(4.0%)	0.083
Asymptomatic	48(10.3%)	32(7.9%)	0.003
Comorbidities, n(%)			
Hypertension	283(60.5%)	169(41.8%)	< 0.001
Overweight	47(10.0%)	40(9.9%)	0.483
Diabetes Mellitus	96(20.5%)	66(16.3%)	0.011
Bronchial asthma	109(23.3%)	28(6.9%)	< 0.001
Hypothyroidism	49(10.5%)	58(14.4%)	0.117
Cardiovascular disease	185(39.5%)	38(8.1%)	< 0.001
Cancer	23(4.9%)	17(4.2%)	0.538
COPD	89(19.0%)	21(5.2%)	< 0.001
Laboratory, mean ±SD(IQR)			
C-reactive protein (mg/l)	66.4 ± 16.5(29.6 − 151.2)	31.4 ± 13.2(20.3 − 73.8)	< 0.001
Ferritin (μg/1)	273.4 ± 42.2(173.2 − 751.3)	113.1 ± 27.2(52.1 − 378.3)	< 0.001
D-dimer (mg/l)	4.3 ± 1.4(1.9 − 7.6)	1.6 ± 0.6(0.9 − 2.7)	< 0.001
SaO_2(%)	71.1 ± 15.1 (51.3-88.4)	88.3 ± 8.9(68.4 − 99.1)	< 0.001
WBC ($\times 10^3/\mu$l)	11.8 ± 5.3(6.5 − 16.1)	7.7 ± 3.0(4.0 − 14.2)	< 0.001
Thrombocyte ($\times 10^3/\mu$l)	171.4 ± 44.6(116.7 − 269.2)	206.4 ± 51.4 (135.3-278.4)	< 0.001
Lymphocyte ($\times 10^3/\mu$l)	0.8 ± 0.4(0.5 − 1.7)	1.0 ± 0.2(0.8 − 1.8)	0.082
Neutrophil ($\times 10^3/\mu$l)	6.8 ± 1.3(3.6 − 8.9)	3.2 ± 1.0(1.8 − 5.2)	< 0.001
Haemoglobin (g/dl)	11.2 ± 1.9(8.7 − 13.9)	12.5 ± 2.4(10.0 − 15.9)	0.002
Handgrip strength (kg)			
Males	13.1 ± 6.8(10.0 − 26.4)	21.3 ± 6.7(12.1 − 36.2)	< 0.001
Females	11.2 ± 4.6 (9.5-19.4)	17.0 ± 4.2(12.1 − 29.1)	< 0.001
Total	12.2 ± 4.5(9.5 − 26.4)	19.2 ± 5.3(12.1 − 36.2)	< 0.001
Low grip strength, n(%)			
Males	177(57.1%)	42(30.2%)	< 0.001
Females	68(43.0%)	71(26.8%)	< 0.001
Handgrip endurance time (sec)			
Males	12.7 ± 4.1(4.1 − 24.0)	21.4 ± 4.9(12.3 − 29.1)	< 0.001
Females	6.1 ± 3.4(2.8 − 13.9)	11.2 ± 3.0(3.9 − 20.1)	< 0.001

Note: BMI; body mass index, IQR; interquartile range, WBC; white blood cell, COPD; Chronic obstructive pulmonary disease. Bold indicates statistically significant variables (p<0.05).

The results of various feature selection technique by Pearson's correlation coefficient (P) is presented in Table 2. The results of the feature selection technique revealed that "COPD", "LGS", "SaO_2", "ET", "CRP", and "Age" can also be significant features for COVID-19 mortality in elderly patients admitted to ICU. We used a decreasing order approach to arrange features and select the best subset of features in the filter-based method. Thus, tests were implemented at first for all possible compounds including top 8, top 7, top 6, top 5, top 4, top 3, and top 2. This approach leads to assigning different ranks to different features by feature selection techniques of Pearson's correlation coefficient (P). The findings illustrated that when Pearson's correlation coefficient (P) is used as the principal criterion, "COPD" is considered the most reliable factor. Similarly, "LGS" is assigned the second rank related to COVID-19 mortality, if P is used as the principal criteria.

To study and confirm the impact of these features on COVID-19 mortality, k-nearest neighbors (K-NN) were evaluated as discussed in Table 3. It is observed that when "COPD", "LGS", "SaO_2", "CRP", and "ET" were used as features, the k-NN classifier achieved the highest classification accuracy of 95.21% under 10-fold cross-validation. This shows that chronic obstructive pulmonary disease (COPD), low grip strength (LGS), SaO_2, C-reactive protein (CRP), and endurance time (ET) together can have a significant impact on the prediction of COVID-19 mortality in elderly patients admitted to ICU using k-NN algorithm.

Table 2. Results of various feature selection techniques.

Feature selection technique	Selected features in decreasing order of their rank (filter method)
P	**COVID-19 $_{\text{Mortality}}$:** COPD, LGS, SaO_2, CRP, ET, Age, Gender, Hypertension, DM, Bronchial asthma, D-dimer, WBC, Thrombocyte, Smoking, Cough, Fever, Dyspnea, Anosmia/ageusia, Asymptomatic, Ferritin, Neutrophil, Haemoglobin, Hospital stay in ICU.

Note: P: Pearson's correlation coefficient, **COPD:** chronic obstructive pulmonary disease, **LGS:** low grip strength, **SaO_2:** oxygen saturation, **ET:** endurance time, **CRP:** C-reactive protein, **WBC:** white blood cell, **DM:** diabetes Mellitus.

Table 3. Impact of COPD, LGS, SaO_2, CRP and ET on COVID-19 mortality prediction using k-NN algorithm under 10-fold cross-validation.

Classification technique	Accuracy (%)	Sensitivity (%)	Specificity (%)	Precision (%)	F1-score	AUC
k-NN	95.21	96.47	95.31	97.32	0.97	0.95

Notes: COPD: chronic obstructive pulmonary disease, **LGS:** low grip strength, **SaO_2:** oxygen saturation, **CRP:** C-reactive protein, **ET:** endurance time, **k-NN:** k-nearest neighbors, **AUC:** area under the curve.

DISCUSSIONS

In this prospective observational cohort study, we aimed to evaluate the HGS and muscular ET among elderly patients with COVID-19 infection admitted to ICU and investigate the possible relationship between HGS and muscular ET with COVID-19 mortality among elderly patients. To the best of our knowledge, this is the first study to demonstrate the prognostic relationship between muscle strength and muscular endurance time in elderly patients who died due to the COVID-19 infection.

In the present study, a database of clinical and biomechanical biomarkers and underlying comorbidities were captured and utilized for COVID-19 mortality prediction. The expected results of the present study reflected that COVID-19 disproportionately endangers elderly patients, especially those with at least one underlying comorbidity (Flaherty et al., 2020). The most common COVID-19-related symptoms in the present study were fever (67.3%), dyspnea (54.8%), and cough (50.2%) consistent with the pertinent studies (Kabeerdoss et al., 2021; Marin et al., 2021). As seen in our patients, studies indicate that older patients aged $\geq$65 years with underlying comorbidities such as hypertension, DM, obesity, bronchial asthma, COPD, and CVD mainly experience more serious consequences and even higher mortality in the ICUs (Onder et al., 2020; Woolf et al., 2021). The present study findings showed that hypertension (60.5%), cardiovascular disease (39.5%), bronchial asthma (23.3%), and diabetes mellitus (20.5%) were the most common comorbidities among the deceased elderly patients, respectively.

Based on the results of feature selection techniques, 23 out of 31 clinical and biomarker features were used for classification. The results showed that the top five features i.e. chronic obstructive pulmonary disease (COPD), low grip strength (LGS), SaO_2, C-reactive protein (CRP), and endurance time (ET) selected by P achieved the highest classification accuracy among all the possible combinations and were used for classification. Meanwhile, our findings showed that the classification accuracy drops when only the top 4 features were considered. Considering these five features for classification made the accuracy of the k-NN classifier reach 95.21% under the 10-fold cross-validation protocol, which is even higher than the case where 6 features are considered. To be more precise, insignificant and irrelevant features may mislead the classifier model and eventually lead to a decrease in its overall performance. In line with the present study, Onder et al. (2020) and Woolf et al. (2021) stated that underlying comorbidities such as bronchial asthma and COPD can be considered the most important predictors of COVID-19 mortality in elderly patients admitted to the ICUs (Onder et al., 2020; Woolf et al., 2021) Our findings have shown that other than well-known and common clinical risk factors, LGS and muscular ET should be considered as independent predictors of COVID-19 mortality in elderly patients. The present study revealed that deceased patients (in both genders) had lower grip strength and muscular ET as well as higher frequency of LGS as compared to survived ones. In line with the present study, Kara et al. (2021) study on COVID-19 patients aged 21–74 years showed that the LGS can be considered as a significant component in severity prediction of COVID-19 infection

(Kara et al., 2021). Sevilla et al. (2022) and Vincenzo Galluzzo (2022) concluded that low HGS and muscular ET independently increased the length of ICU stay and disease severity in elderly patients with COVID-19 (Galluzzo et al., 2022; Sevilla and Sánchez-Pinto, 2022).

The current investigation has a few limitations to note. First, the present study includes the lack of information on the past medical history of patients before acute COVID-19 infection and admission to the ICU. Second, several variables such as dietary habits, lifestyle, physical activity, anthropometric data, maturity stages, the effects of the COVID-19 variants, and SARS-CoV-2 vaccination were not considered, which can be regarded as a reasonable limitation due to the potential for misinterpretation.

CONCLUSION

In this study, we managed to use clinical and biomechanical biomarkers as well as underlying comorbidities for COVID-19 mortality prediction in elderly patients admitted to ICU using K-Nearest Neighbors (k-NN), as a most popular supervised classifier in ML. Results of statistical significance analysis and feature selection techniques indicate that five clinical and biomechanical features including chronic obstructive pulmonary disease (COPD), low grip strength (LGS), SaO_2, C-reactive protein (CRP), and endurance time (ET) have the potential to be used as reliable components for the prediction of COVID-19 mortality in elderly patients. Using machine learning (ML) algorithms with the highest accuracy in determining the contributory clinical and biomechanical features for COVID-19 mortality prediction will enhance the effectiveness of clinical practices and interventions during the pandemic and will reduce the wastage of financial and human resources.

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