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Risk Stratification in Early COVID-19 and Its Predictive Power for Hospitalized Fatality

Hamed Tabesh[1,2], Maryam Rastegar[3], Azadeh Saki[2]*

1. Patient Safety Research Center, Clinical Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran.
2. Department of Biostatistics, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran.
3. Infectious Diseases and Tropical Medicine Research Center, Research Institute of Cellular and Molecular Sciences in Infectious Diseases, Zahedan University of Medical Sciences, Zahedan, Iran.

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ABSTRACT

Background:
Accurate assessment of COVID-19 severity is essential for predicting patient outcomes, enabling clinicians to identify individuals at high risk of fatality early in the disease course. This prognostic information serves to guide triage decisions, ensuring that limited hospital resources are effectively allocated to those in greatest need.

methods:
This retrospective study included 160 hospitalized patients with confirmed COVID-19, aged 18 years and older, who were admitted to hospitals in Iranshahr during 2020. Comorbidities, social and behavioral variables were incorporated into an Artificial Neural Network (ANN) model to predict the severity and fatality of COVID-19.

Results:
The overall in-hospital fatality rate was 14.4%, with all deaths occurring within the critical group. Among demographic factors, older age and lower educational level were significantly associated with increased disease severity (P<0.01), whereas sex and occupational status showed non-significant trends. Regarding behavioral factors, smoking exhibited a positive but statistically non-significant association with COVID-19 severity (P=0.067), while lower fruit consumption was significantly associated with more severe outcomes (P=0.021). Among comorbidities, cancer, hypertension, and cardiovascular disease were strongly associated with severe and critical illness (P<0.05). The ANN analysis revealed that the national COVID-19 severity protocol possesses exceptional predictive power for fatality (AUC = 0.99, 95% CI: 0.98–1.00).

Conclusions:
The findings of this study highlight the critical role of national protocols in optimizing patient triage and hospitalization priorities, and suggest that clinical measures should be integrated with a comprehensive understanding of the social and behavioral factors influencing severity and fatality.

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***Corresponding Author:**
Department of Epidemiology and Biostatistics, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran E-mail: sakia@mums.ac.ir

Introduction

Accurate assessment of COVID-19 severity is essential for predicting patient outcomes, as it allows clinicians to identify individuals at high risk of mortality early in the disease course. This prognostic information directly guides triage decisions, ensuring that limited hospital resources, especially ICU beds, ventilators, and specialized staff, are allocated to those who need them most. By systematically stratifying patients based on clinical, laboratory, and imaging indicators of severity, healthcare systems can reduce preventable deaths and deliver timely, risk-appropriate care during surges of infection. Six years after the onset of the COVID-19 pandemic, its enduring impact continues to pose a major health challenge in primary care. WHO sentinel data show that by mid-May 2025, the global COVID-19 test positivity rate had reached 11%, equaling the previous year's peak observed in July 2024 (1, 2). Numerous studies have described the clinical manifestations of COVID-19 among hospitalized patients across different countries (3). In Iran, national protocols for hospitalization and severity assessment have established standardized categories of illness, including moderate, severe, and critical stages. While these classifications guide clinical management and resource allocation, there has been limited investigation into their analytic use for predicting patient outcomes. Specifically, no studies have examined risk factors for disease severity across these ordered categories under the national severity protocol, nor assessed how they contribute to outcome prediction. Understanding these associations is essential for improving triage decisions and enhancing the accuracy of prognosis models in the Iranian healthcare context (4, 5).

Although vaccination and therapeutic advancements have reduced overall mortality, a wide spectrum of clinical responses persists, ranging from asymptomatic infections to severe and critical illness. Understanding why some individuals experience milder disease outcomes upon exposure while others require intensive care is crucial. Identifying the risk factors that determine disease severity allows clinicians to screen vulnerable patients earlier and implement more tailored treatment protocols.

COVID-19 has posed an unprecedented challenge to healthcare systems globally, particularly due to its heterogeneous clinical course and unpredictable progression. Therefore, identifying determinants of disease severity using appropriate statistical models is essential for improving early risk stratification and clinical decision-making (6-8).

An extensive body of scientific literature exists regarding the predictors of COVID-19 severity. While certain factors, such as age and pre-existing conditions, are consistently recognized as strong determinants, the role of behavioral and demographic factors often requires nuanced statistical evaluation. Consistently, increasing age has been identified as the strongest predictor of adverse outcomes and greater disease severity (Severe/Critical). This is attributed to factors like immune-senescence and the higher prevalence of chronic diseases in older populations. Furthermore, some studies have indicated that sex may act as a modifying factor, with males tending to exhibit more severe outcomes in certain populations (9-11).

In addition, Comorbidities play a vital role. Research has extensively demonstrated that a history of Diabetes Mellitus, Cardiovascular Diseases, Hypertension, Obesity (high BMI), and chronic respiratory diseases (e.g., COPD) are significantly associated with an increased risk of hospitalization and disease progression (3).

The impact of lifestyle factors is more complex, with some studies reporting mixed or nuanced results. While extreme obesity (BMI ≥40) is a known risk factor for hospitalization and mechanical ventilation, some literature suggests that in younger populations or among those who become critically ill, obesity might show a weaker correlation with severity compared to other variables, or even exhibit a temporary protective effect in very early infection stages (Obesity Paradox), though this is not confirmed for later, severe stages (12-14).

The scientific consensus on smoking and COVID-19 severity remains ambiguous. Some early studies provided stronger evidence linking smoking to severe outcomes, while larger, more controlled studies have reported weak or non-significant statistical associations (often with P-values close to the 0.05 threshold). These discrepancies may stem from differences in how smokers (current, former, or intensity of use) are categorized (13, 15-17).

The role of dietary habits has received less direct investigation. However, recent evidence underscores the importance of nutrient-rich diets. Findings that link low Fruit consumption to higher disease severity suggest a hypothesis that a deficiency in antioxidants and vitamins might modulate the body's inflammatory response in a way that predisposes to more severe outcomes (18).

Identifying key factors associated with the severity of COVID-19 can play a crucial role in improving patient management and optimizing the allocation of hospital resources. Such knowledge enables healthcare providers to identify high-risk patients at an early stage and make more informed clinical decisions regarding hospitalization, level of care, and therapeutic interventions. Moreover, understanding these factors provides an evidence-based foundation for the efficient distribution of critical resources, including intensive care unit beds, ventilators, and medical staff. Ultimately, this information can enhance health system preparedness and response in future pandemics with similar characteristics, leading to better patient outcomes and reduced strain on healthcare systems (19).

An important conceptual and methodological consideration in the present study is the explicit treatment of COVID-19 severity as an ordered clinical outcome rather than a dichotomous endpoint such as survival or ICU admission. National guidelines classify hospitalized patients into moderate, severe, and critical categories, reflecting a clinically meaningful progression of disease rather than discrete, unrelated states. Modeling severity across these ordered levels allows for a more nuanced evaluation of factors associated with disease progression, preserves information that is lost in binary classifications, and better mirrors real-world clinical decision-making and resource allocation. Within this framework, increasing attention has been drawn to the contribution of social determinants of health, including education, occupation, and health-related behaviors, which may influence exposure risk, healthcare access, timing of presentation, and underlying vulnerability to severe disease. The aim of the current investigation, utilizing Machine Learning models, specifically Artificial Neural Networks (ANN), to evaluate whether a combination of these behavioral and demographic factors can accurately predict disease severity and to determine which model is most suitable for this classification task.

Methods

Data for this study were collected from all 169 hospitalized COVID-19 patients presenting during the first peak of the pandemic in 2020 at medical centers affiliated with Iranshahr University of Medical Sciences. After excluding under eighteen years old cases, a total of 160 adult patients were included. Patient severity was classified at the time of admission into Moderate, Severe, or Critical categories, adhering strictly to the guidelines issued by the Deputy Ministry of Health and Treatment. Data extracted from registry forms included socio-demographic factors, behavioral data, and a checklist of comorbidities. The primary outcomes of interest were overall disease severity and in-hospital fatality. To analyze the influence of various factors, two distinct ANN

architectures were developed: Model I (focused on clinical comorbidities) and Model II (focused on socio-demographic and behavioral variables). The relationship between these independent variables and the outcomes (severity and fatality) was characterized using ROC curve analysis and normalized importance statistics. The performance of the models was evaluated using confusion matrices, Cross-Entropy loss, and the Area Under the Curve (AUC). To mitigate the risk of overfitting, the data were split into training and testing sets. The model architecture comprised an input layer consisting of independent variables, including demographic, social, and behavioral factors. A single hidden layer was utilized, containing one unit with a hyperbolic tangent activation function to facilitate non-linear mapping. The output layer was configured with three units, corresponding to the three levels of disease severity, employing a Softmax activation function to generate class probabilities. Model training was optimized using the cross-entropy loss function to minimize classification error. Following standard practice, the bias units were excluded from the structural description provided herein.
Also, to determine the influence of various factors on fatality of COVD-19, two distinct ANN models were developed: one for socio-behavioral variables and another for comorbidities. The model architecture comprised an input layer consisting of independent variables, including demographic, social, and behavioral factors. A single hidden layer was utilized, containing one unit with a hyperbolic tangent activation function to facilitate non-linear mapping. The output layer was configured with two units, corresponding to the two levels of disease fatality, employing a sigmoid activation function to generate class probabilities. Model training was optimized using the cross-entropy loss function to minimize classification error.

Results

Of the 160 hospitalized patients admitted to hospitals, 137 patients (85.6%) recovered, whereas 23 patients (14.4%) died. Table 1, shows that the fatality has very strong and highly significant association with disease severity ($P < 0.001$), such that all deceased patients were classified in the critical group, whereas surviving patients were predominantly observed in the moderate and severe categories.
Among the studied patients, 96 individuals (60%) had negative PCR results, 32 patients (20%) tested positive, and 32 patients (20%) did not undergo PCR testing. Considering that out of 128 hospitalized COVID-19 patients with PCR test results, 96 had negative PCR results, the probability of a false-negative PCR test was estimated to be 0.75, indicating an approximate false-negative rate of 75%.

Evaluation of chest radiographic findings revealed that 14 patients (8.3%) had normal imaging, 40 patients (25%) showed unilateral patchy infiltration, 77 patients (48.1%) exhibited bilateral patchy infiltration, and 30 patients (18.7%) presented with advanced pulmonary involvement characterized by extensive ground-glass opacities. Overall, 91.9% of chest imaging findings were consistent with COVID-19 infection.

Statistical analysis of the three main variables associated with COVID-19 disease severity categories yielded the following results. PCR test results showed no statistically significant association with disease severity ($P = 0.680$), indicating that PCR implementing, positivity or negativity had no meaningful impact on the clinical severity of the disease. In contrast, chest CT findings demonstrated a strong and statistically significant positive association with disease severity ($P < 0.001$).

Also, the results of analysis of underlying medical conditions with COVID-19 severity showed in table1. Among all assessed comorbidities, only a history of cardiovascular disease and hypertension was strongly and statistically significantly associated with increased COVID-19 disease severity ($P < 0.001$ for both). Patients with pre-existing cardiovascular disease or hypertension exhibited a markedly higher proportion of severe and critical illness compared with those without these conditions. For example, among individuals with hypertension, 39.0% were classified as having critical disease, whereas only 10.1% of patients without hypertension fell into the critical category.

Table 1. Statistical association between Fatality, diagnostic markers (PCR, CT), and comorbidities with the levels of COVID-19 disease severity

		COVID-19 severity N (row percent)				
		Moderate	Severe	Critical	Total	P-value
Fatality		-	-	23 (100.0)	23	< 0.001
PCR	Negative	42 (43.8)	38 (39.6)	16 (16.7)	96	0.680
	Positive	15 (46.9)	13 (40.6)	4 (12.5)	32	
	Not done	17 (53.1)	7 (21.9)	8 (25.0)	32	
Chest CT	Normal	10 (76.9)	3 (23.1)	0 (0.0)	13	< 0.001
	Infiltration patchy-one	27 (67.5)	9 (22.5)	4 (10.0)	40	
	Infiltration patchy-two	27 (35.1)	36 (46.8)	14 (18.2)	77	
	Spread	10 (33.3)	10 (33.3)	10 (33.3)	30	
Comorbidities	HIV	1 (33.3)	2 (66.7)	-	3	
	Heart Disease	8 (22.2)	15 (41.7)	13 (36.1)	36	< 0.001
	Hypertension	14 (34.1)	11 (26.8)	16 (39.0)	41	< 0.001
	Thyroid	3(100.0)	-	-	3	0.095
	Diabetes	6 (28.6)	13 (61.9)	2 (9.5)	21	0.523
	Kidney Disease	7 (46.7)	5 (33.3)	3 (20.0)	7 (46.7)	0.91
	Asthma	3 (42.9)	3 (42.9)	1 (14.3)	7	0.995
	Respiratory Disease	6 (46.2)	4 (30.8)	3 (23.1)	13	0.775
	Liver Disease	2 (40.0)	3 (60.0)	-	5	0.732
	Cancers	-	1 (33.3)	2 (66.7)	3	0.026
	Hepatitis	3	-	-	3	0.095
	Psychological Disease	4 (66.7)	-	2 (33.3)	6	0.878
	BMI ≥ 40	-	1 (50.0)	1 (50.0)	2	0.134
Total		74 (46.3)	58 (36.3)	28 (17.5)	160	

In addition, a history of cancer showed a statistically significant association with disease severity (P = 0.026). Although the number of patients with cancer was limited, 66.7% of these patients were classified as having critical illness, indicating a substantially elevated risk of severe outcomes in this subgroup.

In contrast, other comorbid conditions, including HIV infection, thyroid disorders, diabetes mellitus, chronic kidney disease, asthma, chronic respiratory diseases, liver disease, hepatitis, and other neurological or systemic disorders did not demonstrate statistically significant associations with COVID-19 disease severity, as reflected by P-values greater than 0.05. These findings suggest that, within this study population, the presence of cardiovascular disease, hypertension, and cancer played a more prominent role in determining clinical severity than other underlying health conditions. In addition, severe obesity (BMI ≥ 40 kg/m^2), was not significantly related to disease severity (P = 0.134).

Analysis of demographic characteristics (Table 2) demonstrated that marital status and religious affiliation were not significantly associated with COVID-19 disease severity (P = 0.995 and P = 0.873, respectively). The distribution of patients across moderate, severe, and critical categories was largely uniform among different marital and religious subgroups, indicating no meaningful relationship between these variables and clinical severity.

With respect to sex, although the association did not reach conventional statistical significance (P = 0.098), a borderline trend was observed. Male patients exhibited a higher proportion of critical illness compared with female patients (23.5% vs. 11.4%), suggesting a potential sex-related difference in disease progression that did not achieve statistical significance in the present sample. In contrast, age groups showed a statistically significant association with disease severity (P = 0.020). An evident gradient toward more severe clinical outcomes was observed with increasing age. Younger patients aged 18–30 years were predominantly classified as having moderate disease (55.6%), whereas older age groups had the highest proportions of severe and critical disease, highlighting age as a key determinant of COVID-19 severity.

Occupation was not significantly associated with disease severity (P = 0.075). However, the distribution observed among employees, in whom the majority of cases were classified as moderate (84.6%), should be interpreted cautiously due to the small sample size in this subgroup (n = 13). This disproportionate distribution is likely attributable to sampling variability rather than reflecting a true protective occupational effect. Educational level demonstrated a statistically significant association with COVID-19 severity (P = 0.010). Patients with primary education were most frequently classified as having moderate disease (62.8%), whereas illiterate individuals exhibited the highest proportions of severe (43.9%) and critical (28.1%) illness. These findings suggest that lower educational attainment may be associated with an increased likelihood of experiencing more severe COVID-19 outcomes in this study population Analysis of behavioral factors indicated that most of the variables examined were not significantly associated with COVID-19 disease severity, with the notable exception of fruit consumption (Table 2). Hookah use showed no statistically significant association with disease severity (P = 0.775), as the distribution of moderate, severe, and critical cases among hookah users was comparable to that observed among non-users. Similarly, drug use was not significantly associated with disease severity (P = 0.098), although a higher proportion of severe and critical cases was observed among drug users compared with non-users, suggesting a non-significant upward trend toward more severe outcomes. Cigarette smoking likewise demonstrated no statistically meaningful association with disease severity (P = 0.067).

In contrast, fruit consumption exhibited a statistically significant association with COVID-19 severity (P = 0.021). Patients reporting the lowest level of fruit intake had the highest combined proportion of severe and critical illness (57.6%), whereas those with the highest level of fruit consumption were predominantly classified as having moderate disease (75.0%) and showed the lowest proportion of severe and critical cases (25.0%). These findings suggest a potential protective association between higher fruit intake and reduced COVID-19 severity in this study population.

Table 2. Association between Demographic and Behavioral factors with COVID-19 Severity

Demographic factors		**COVID-19 severity** N (Row Percent)			**Total**	**P-Value**
		moderate	sever	critical		
Marital	Single	10 (45.5)	8 (36.4)	4 (18.2)	22	0.995
	Married	64 (46.4)	50 (36.2)	24 (17.4)	138	
Sex	Female	37 (46.8)	33 (41.8)	9 (11.4)	79	0.098
	Male	37 (45.7)	25 (30.9)	19 (23.5)	81	
Religious	Sunni Muslims	51 (47.7)	38 (35.5)	18 (16.8)	107	0.873
	Shia Muslim	23 (43.4)	20 (37.7)	10 (18.9)	53	
Age Groups	18-30	20 (55.6)	13 (36.1)	3 (8.3)	36	0.020*
	30-45	19 (45.2)	15 (35.7)	8 (19.0)	42	
	45-60	20 (54.1)	12 (32.4)	5 (13.5)	37	
	60-75	10 (38.5)	10 (38.5)	6 (23.1)	26	
	+75	5 (26.3)	8 (42.1)	6 (31.6)	19	
Job	Employee	11 (84.6)	1 (7.7)	1 (7.7)	13	0.075
	Freelancer	18 (52.9)	9 (26.5)	7 (20.6)	34	
	Unemployed	29 (39.2)	32 (43.2)	13 (17.6)	74	
	other	16 (41.0)	16 (41.0)	7 (17.9)	39	
Education	Illiterate	16 (28.1)	25 (43.9)	16 (28.1)	57	0.010*
	Primary	27 (62.8)	11 (25.6)	5 (11.6)	43	
	Secondary	20 (50.0)	16 (40.0)	4 (10.0)	40	
	University	11 (55.0)	6 (30.0)	3 (15.0)	20	
Fruit	Middle	12 (75.0)	2 (12.5)	2 (12.5)	16	0.021
	Low	40 (43.5)	41 (44.6)	11 (12.0)	92	
	Very Low	22 (42.3)	15 (28.8)	15 (28.8)	52	
Behaviors	Hooka	4 (30.8)	8 (61.5)	1 (7.7)	13	0.775
	Drug user	2 (18.2)	5 (45.5)	4 (36.4)	11	0.098
	Smoking	3 (23.1)	6 (46.2)	4 (30.8)	13	0.067
Total		74 (46.3)	58 (36.3)	28 (17.5)	160	

(Table 3), presented the confusion matrix for prediction vs observed test set by two ANN models. Model I showed excellent performance in identifying moderate cases, correctly classifying all 19 patients in this group with 100.0% accuracy. In addition, Model I demonstrated relatively acceptable discrimination of critical cases, correctly identifying 5 of the 7 true critical patients (71.4%). However, this model failed entirely to identify severe disease, as none of the 17 patients with severe COVID-19 were correctly classified, yielding an accuracy of 0.0% for this category. All severe cases were misclassified as either moderate or critical, indicating a substantial limitation in the model's ability to distinguish intermediate disease severity.

A divergence was observed between the cross-entropy values and the overall error rates of Model I and Model II. While Model I demonstrated higher precision in identifying moderate and critical cases, Model II exhibited superior performance in classifying severe cases. Overall, Model II achieved a lower proportion of incorrect predictions (36.7% vs. 44.2%) and presented a more favorable performance profile in the model summary. Although direct comparisons of cross-entropy are most valid when identical loss functions are applied, the results suggest that Model II provides a more reliable and balanced classification of disease severity across all categories.

Table 3. Results of the ANN for predicting COVID-19 Severity

	Observed	Predicted			Percent Correct	**Model Summary**
		moderate	sever	critical		
Model I	Moderate	19	0	0	100.0%	Cross Entropy= 39.985 Percent Incorrect Predictions= 44.2%
	Severe	13	0	4	0.0%	
	Critical	2	0	5	71.4%	
Model II	Moderate	21	4	1	80.8%	Cross Entropy= 44.530 Percent Incorrect Predictions 36.7%

Model II exhibited a more balanced classification performance across severity levels. This model correctly classified 21 moderate cases, outperforming Model I in this category, and showed a marked improvement in identifying severe disease, correctly classifying nine patients, whereas Model I failed to correctly classify any severe cases. Nevertheless, the principal limitation of Model II was its poor performance in identifying critical cases, the area under the ROC curves for critical cases in model I is AUC=0.688 versus AUC=0.725 for Model II, as shown in (Figure1).

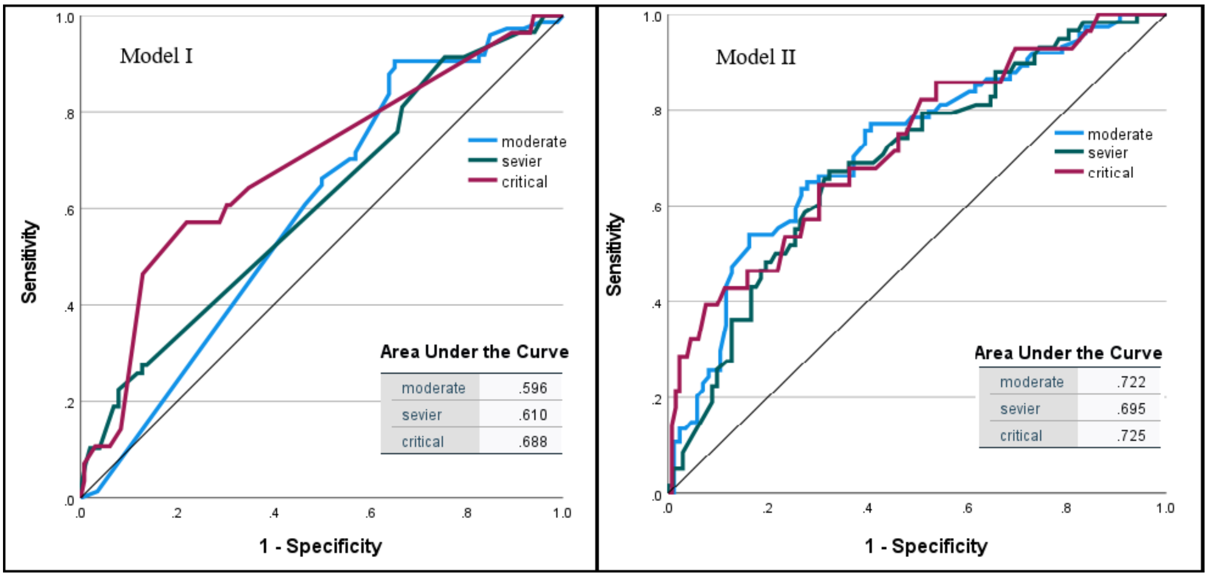

Figure 1. Roc Curves of Model I and Model II for COVID-19 Severity

illustrates the normalized importance of input variables in two artificial neural network models developed to assess factors associated with COVID-19 disease severity. In Model I, which primarily incorporated clinical comorbidities, hypertension emerged as the most influential predictor, exhibiting the highest normalized importance (0.394). This was followed by cardiovascular disease (0.229), indicating a substantial contribution of underlying heart conditions to the model's severity classification. Asthma (0.163) and renal disease (0.120) showed moderate levels of importance, whereas chronic respiratory disease (0.061) and diabetes mellitus (0.034) contributed minimally to the model's predictive structure. These findings suggest that, among comorbidities, vascular and cardiac conditions played a dominant role in driving severity discrimination within Model I, while metabolic disorders such as diabetes had comparatively limited influence. In Model II, which incorporated demographic and behavioral variables, occupational status (job) demonstrated the highest normalized importance (0.214), closely followed by fruit consumption (0.212). This highlights the potential relevance of socioeconomic and lifestyle-related factors in the classification of disease severity. Age (0.146) and educational level (0.137) also exhibited substantial importance, reinforcing the role of older age and lower education in more severe disease outcomes. Gender showed a moderate contribution (0.125), whereas religious affiliation (0.084) and drug use (0.052) had limited influence. Behavioral factors such as smoking (0.016) and hookah use (0.014) demonstrated minimal importance, suggesting a relatively weak contribution to severity classification within this model. (Figure 2).

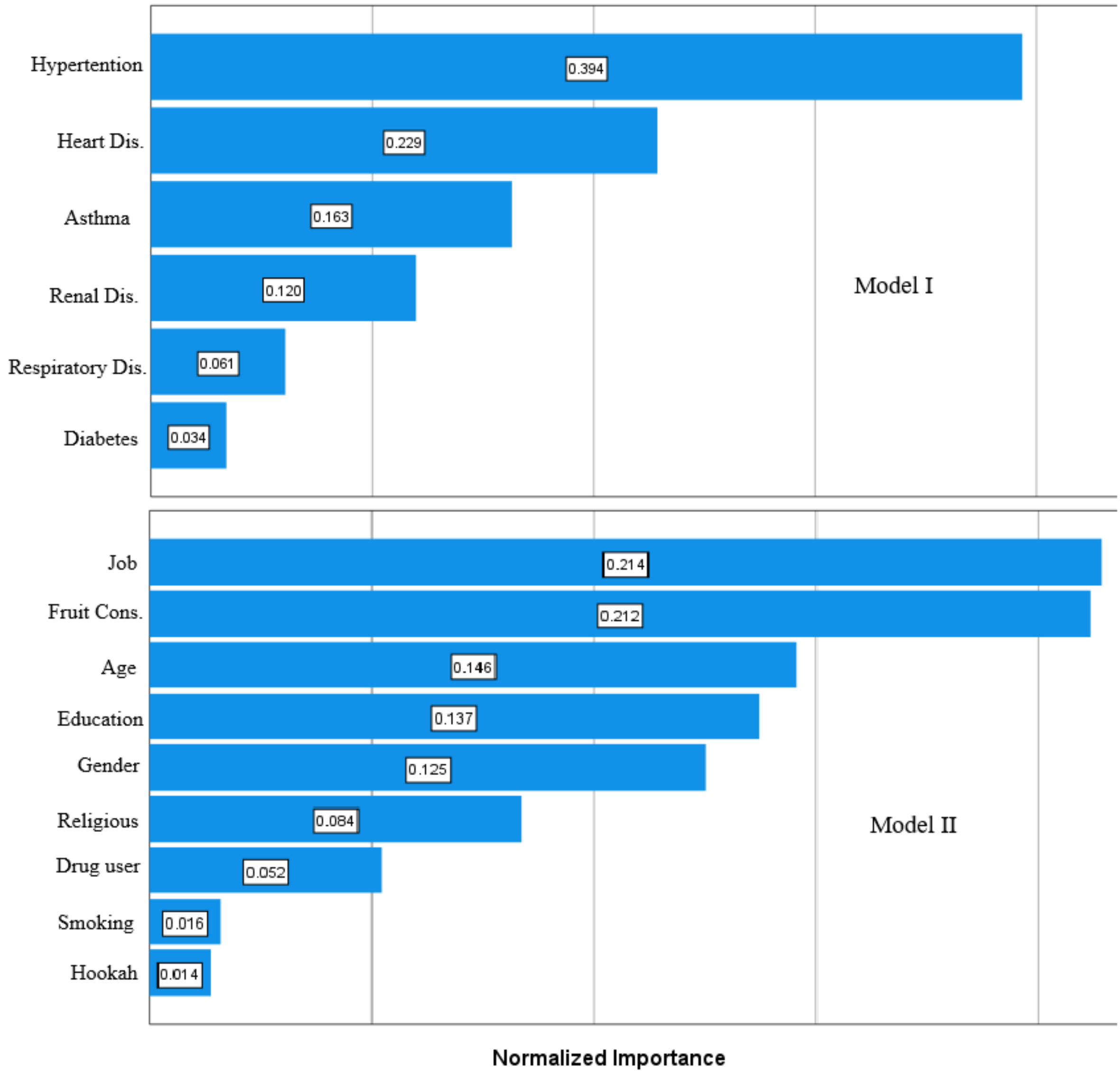

Figure 2. Comparing the importance of factors in Model I and Model II for COVID-19 Severity

presented the confusion matrix for prediction vs observed test set by two ANN models for fatality of COVID-19. Model I showed excellent performance in identifying death, correctly classifying all 10 patients in this group with 100.0% accuracy (Table 4).

Table 4. Results of the ANN for predicting COVID-19 fatality

	Observed	Predicted		Percent Correct	**Model Summary**
		Alive	Death		
Model I	Alive	32	1	97.0%	Cross Entropy= 4.11 Percent Incorrect Predictions=2.3%
	Dead	0	10	100.0%	
Model II	Alive	32	1	97.0%	Cross Entropy Error=8.68 Percent Incorrect Predictions=7.0%
	Dead	2	8	80.0%	

In addition, Model I demonstrated relatively acceptable discrimination of alive patients, correctly identifying 32 of the 33 true critical patients (97%). Model II has not superior performance in classifying COVID-19 death compared with Model I. This model achieved an upper overall proportion of incorrect predictions (7.0% versus 2.3%). Model I, exhibited a more favorable performance profile in the model summary and the area under the ROC curves (AUC=0.994 versus AUC=0.989) as shown in (Figure3).

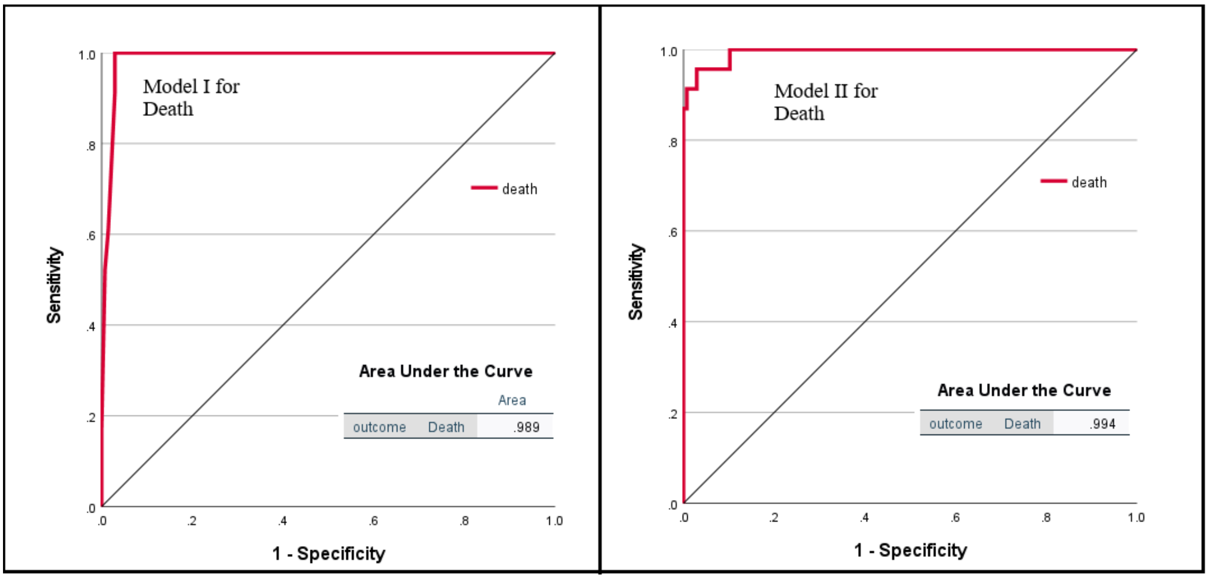

Figure 3. Roc Curves of Model I and Model II for COVID-19 Fatality

illustrates the normalized importance of input variables in two artificial neural network models developed to assess factors associated with COVID-19 fatality. In Model I, which primarily incorporated clinical comorbidities, COVID-19 severity status emerged as the most influential predictor, exhibiting the highest normalized importance. In Model II, which incorporated demographic and behavioral variables, also, COVID-19 severity status demonstrated the highest normalized importance (0.454).

This highlights the potential relevance of COVID-19 severity categorization (Figure 4).

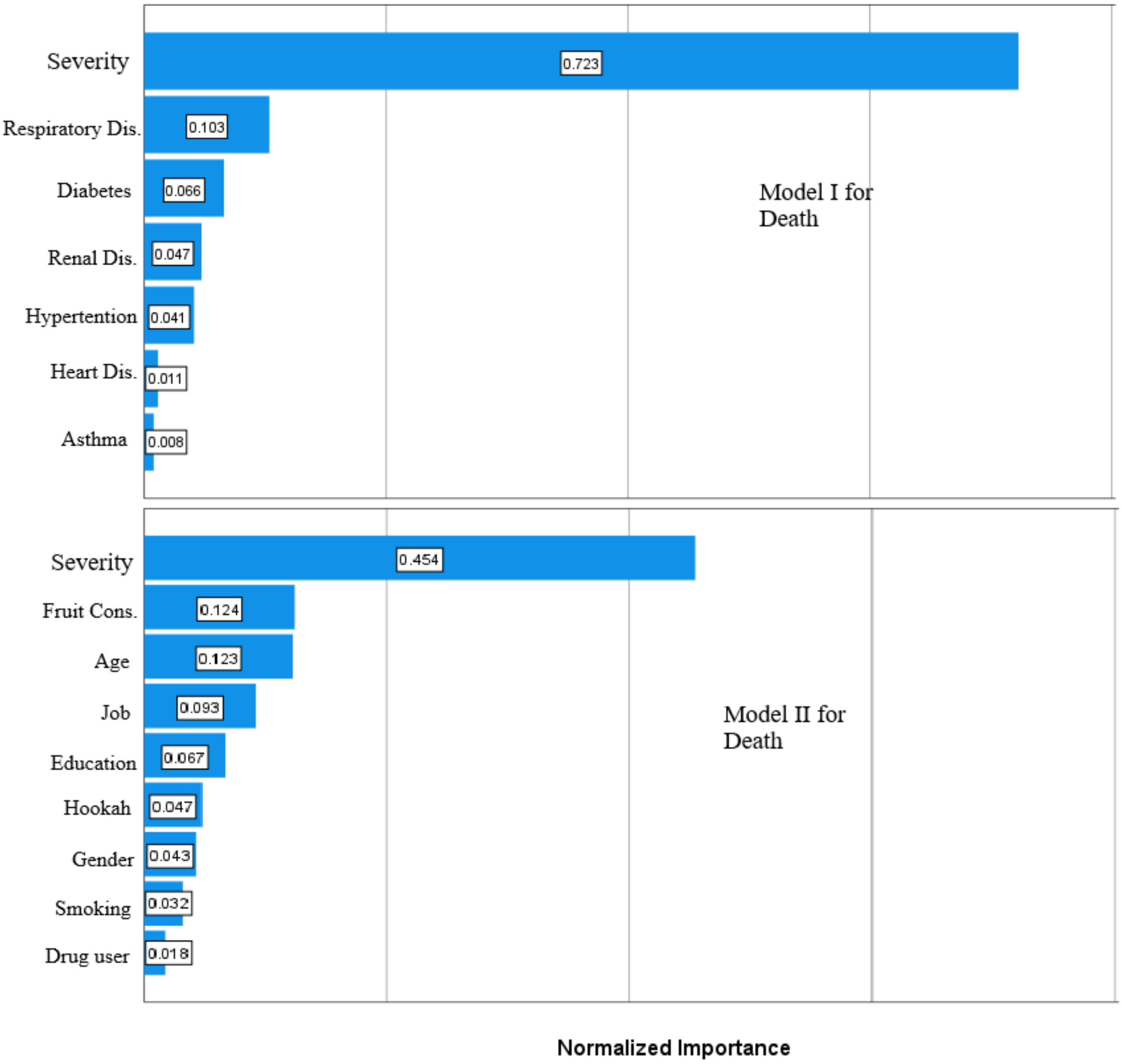

Figure 4. Comparing the importance of factors in Model I and Model II for COVID-19 Fatality

Discussion

In this retrospective study, we investigated factors associated with COVID-19 disease severity using ANN. Our findings demonstrated that chest CT findings, age, and underlying comorbidities were significantly associated with increasing disease severity.

One of the most important findings of this study was the lack of a significant association between PCR test results and disease severity. This observation may be attributed to the high false-negative rate of PCR testing, especially during early disease stages or due to sampling limitations, which has been widely reported in the literature (1, 20-22). In contrast, chest CT findings showed a strong and graded relationship with disease severity, consistent with previous studies indicating that radiological involvement closely reflects pulmonary damage and clinical deterioration (23-26).

The strong association between cardiovascular disease and disease severity observed in our cohort aligns with large-scale studies reporting higher rates of severe outcomes and mortality among patients with underlying cardiovascular conditions. These comorbidities may exacerbate COVID-19 related inflammatory responses and impair physiological reserve, leading to worse clinical outcomes (11, 25, 27).

Furthermore, all deaths in this study occurred among patients classified as critical, reinforcing the clinical relevance of severity classification systems and their utility in predicting outcomes. Similar findings have been reported in large retrospective cohorts from China and Europe (20, 22, 25, 28, 29).

The strength derived from the initial statistical analysis were centered on establishing predictive markers to statistically confirm which factors significantly differentiated between moderate, severe, and critical COVID-19 cases. This successfully identified Age Group (P=0.020) and Education Level (P=0.010) as primary demographic determinants, and Fruit Consumption (P=0.021) as a significant, actionable behavioral determinant. And also, to quantify the role of lifestyle choices (smoking, drug use, hookah) despite their non-significant final outcomes, providing context on factors that might warrant future, larger-scale investigation.

To utilize machine learning (ANNs) to translate these input features into a reliable severity classification system, moving beyond simple statistical association to fond the comprehensive importance of impute features. The decision to employ two distinct ANN architectures (Model I and Model II) and compare their performance offered significant strategic advantages in handling this complex classification problem.

The most crucial strength of using ANNs is their inherent ability to model complex, non-linear relationships between predictors and the outcome. Unlike cumulative logistic regression, ANNs can effectively capture intricate interactions between variables like age, education, and diet, which rarely operate in isolation.

By testing Model I vs. Model II, the strategy allowed for a direct assessment of how architectural differences impact performance metrics such as Cross Entropy (training fit) versus Percent Incorrect Predictions (generalization). This comparative approach is robust, leading to the conclusion that Model II (36.7% Incorrect) offered superior generalization despite potential overfitting concerns in Model I's training error.

Artificial neural network models were also explored as a complementary analytical approach. Although these models demonstrated moderate predictive performance, they showed clear limitations in accurately distinguishing between severe and critical cases. Importantly, however, the primary aim of this study was not to develop or optimize a predictive classification model, but rather to identify and evaluate key factors associated with COVID-19 disease severity using appropriate statistical methods (5, 7, 30). Therefore, the ANN findings should be interpreted as supplementary and exploratory, rather than as a central component of the study's conclusions.

We acknowledge a limitation regarding "circular reasoning" in the fatality model, as "Severity Status" is a primary predictor of death. In this context, the ANN results should be interpreted as a validation of the national severity protocol's predictive power rather than the discovery of new independent predictors. Furthermore, the limited sample size (n=160) and small number of events (23 deaths) may increase the risk of overfitting. The difficulty the models had in distinguishing between "severe" and "critical" cases suggests these categories share overlapping clinical features.

Despite these limitations, the high AUC for fatality prediction reinforces the clinical relevance of the severity categorization. This study serves as an exploratory pilot that underscores the necessity of implementing national protocols to streamline hospitalization prioritization for COVID-19 patients, while simultaneously addressing the behavioral and social determinants that influence disease severity and mortality rates.

Conclusion

This study represents a critical validation of the clinical triage process. Our findings demonstrate that while individual comorbidities, demographics, and behavioral factors are significantly associated with disease severity, they possess limited independent predictive power for severity and fatality. In contrast, the national severity categorization protocol exhibited exceptionally high predictive accuracy. This disparity highlights that the national protocol successfully integrates multiple complex clinical indicators into a single, actionable metric, underscoring its necessity for effective patient triage and resource prioritization.

Results of this study demonstrates that combining clinical and socio-behavioral factors enhances the accuracy and efficacy of risk stratification. We recommend that clinicians integrate social risk factors into their triage process to identify vulnerable patients earlier. Further research with larger cohorts and external validation is required to refine these models for clinical implementation.

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Abbreviation

ANN: Artificial Neural Network; AUC: Area Under Curve; ROC: Receiver Operating Characteristic; CT: Computerized Tomography; PCR: Polymerase Chain Reaction; BMI: Body Mass Index.

Ethical Approval

The study protocol was approved by Research Ethics Committee of Mashhad University of Medical Sciences with the reference number: IR.MUMS.REC.1401.271, and adhered to the principles of the Declaration of Helsinki.

Privacy Statement

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Competing interests

The authors declare that they have no competing interests.

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