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Clinical Characteristics Associated with RT-PCR Positivity Among Patients Suspected of COVID-19 and In-Hospital Mortality Among Patients with Confirmed COVID-19

Gholamreza Bazmandegan[1, 2], Fatemeh Amin[1, 2], Fatemeh Bahrehmand[3], Zeinab Moinfar[4], Zahra Kamiab[1, 5]*

[1]Physiology-Pharmacology Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran; [2]Department of Physiology and Pharmacology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran; [3]Department of Internal Medicine, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran; [4]Department of Public Health and Preventive Medicine, NOSM University, Sudbury, ON, Canada; [5]Department of Community Medicine, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

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***Correspondence**
Email: dr.kamiab89@gmail.com

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ABSTRACT

Introduction: Identifying clinical characteristics associated with a positive reverse transcription polymerase chain reaction (RT-PCR) result and in-hospital mortality may improve repeat-testing strategies, patient screening, and timely clinical management. This study aimed to identify factors associated with RT-PCR positivity among patients with suspected COVID-19 and factors associated with in-hospital mortality among patients with confirmed COVID-19. **Methods:** This retrospective observational study included 505 hospitalized patients with suspected or confirmed COVID-19 admitted to Ali-Ibn Abi-Talib Hospital, Rafsanjan, Iran, between April and July 2022. Demographic and clinical data, RT-PCR results, and outcomes were extracted from medical records. Associations with RT-PCR positivity were examined using univariable logistic regression and least absolute shrinkage and selection operator (LASSO) variable selection, followed by an unpenalized multivariable logistic regression model refitted using the selected variables. Predictive patterns and pairwise combinations associated with mortality among RT-PCR-positive patients were explored descriptively using Multifactor Dimensionality Reduction (MDR). Statistical analyses were performed using SPSS version 19, R version 3.6.3, and Python with the scikit-mdr package. **Results:** The mean age was 54.7 ± 20.4 years, and 52.3% of patients were male. Overall, 259 (51.3%) patients had positive RT-PCR results, among whom 30 (11.6%) died. In the refitted, post-selection model, cough (odds ratio [OR] = 1.66, 95% confidence interval [CI]: 1.13–2.44), myalgia (OR = 1.60, 95% CI: 1.08–2.38), hypertension (OR = 1.90, 95% CI: 1.05–3.51), and intubation (OR = 2.94, 95% CI: 1.41–6.33) were associated with a positive RT-PCR result, whereas cardiovascular disease and admission to the general ward or intensive care unit (ICU) (*vs.* isolation ward) were associated with lower odds (area under the receiver operating characteristic curve [AUC] = 0.691). In the elderly subgroup, the refitted multivariable model including dyspnea, hypertension, intubation, chronic neurological disease, and chronic kidney disease had an AUC of 0.831. MDR analysis showed that hypertension had the highest single-variable balanced accuracy for mortality (57.6%). Single-variable balanced accuracies for age ≥ 60 years (43.8%) and cough (39.1%) were below the 50% chance benchmark, suggesting unstable or poorly discriminating cross-validated classification rather than reliable effects. **Conclusion:** While cough, myalgia, hypertension, and intubation (a post-admission severity marker) were associated with higher odds of RT-PCR positivity, pre-existing cardiovascular disease and admission to non-isolation wards were associated with lower odds among hospitalized patients suspected of COVID-19. Among patients with confirmed COVID-19, the combination of age ≥ 60 years and cough showed the largest pairwise predictive improvement for in-hospital mortality in the MDR analysis; however, the overall predictive performance of both individual variables and variable combinations remained modest and close to the chance level. These exploratory findings may inform further evaluation of clinical assessment and repeat RT-PCR testing while emphasizing the need for externally validated multivariable prediction models for mortality risk stratification, as the present MDR analysis did not provide a validated mortality risk-stratification tool.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged following an outbreak of pneumonia in Wuhan, China, in late 2019 and rapidly spread worldwide, posing unprecedented challenges to healthcare systems and emerging as a serious global clinical threat [1]. COVID-19 presents with a wide spectrum of clinical manifestations ranging from asymptomatic infection [2] to severe pneumonia and acute respiratory distress syndrome (ARDS) [3]. The main symptoms of COVID-19 include

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fever, cough, fatigue, dyspnea, sore throat, headache, conjunctivitis, and gastrointestinal problems [3]. Early estimates for SARS-CoV-2 infection indicated an incubation period of approximately 2–14 days, with symptom onset commonly around four to five days after exposure; however, the Omicron variant has subsequently been associated with a shorter incubation period than earlier SARS-CoV-2 variants [4]. While the epidemiological characteristics of COVID-19 have been extensively characterized over the course of the pandemic, initial reports from China [5], the United States [6], and Italy [7] highlighted considerable variability in clinical presentations and risk factors associated with increased mortality. In general, older adults and individuals with pre-existing comorbidities, including cardiovascular diseases (*e.g.*, heart failure and coronary artery disease), hypertension, diabetes mellitus, chronic kidney disease, chronic respiratory diseases, immunocompromising conditions, malignancies, and neurological disorders, are recognized as high-risk groups for severe COVID-19 and mortality [8, 9]. Severe COVID-19 can progress to ARDS, an important complication associated with substantial mortality [10].

Mortality estimates for COVID-19 have shown substantial heterogeneity across different populations and time periods, largely due to differences in study design, case definitions, healthcare capacity, and evolving viral variants. The Omicron variant, which became the dominant strain globally in early 2022, has been consistently associated with lower rates of severe disease and mortality compared to earlier variants such as Delta, attributable to both its distinct biological characteristics and the protective effects of vaccination and prior infection [11]. While community-based infection-fatality rates are generally below 1% in vaccinated populations, hospitalized cohorts have reported widely varying mortality rates, which differ substantially by patient selection, clinical severity, vaccination history, and healthcare setting [11].

When the number of infected cases is rapidly increasing, the early identification and prompt isolation of suspected cases are crucial to interrupt the transmission chain. In this regard, diagnostic strategies such as rapid antigen testing, along with preventive measures, may be effective for guiding public health interventions [12]. Reported RT-PCR diagnostic sensitivity and specificity vary according to specimen type, timing of sampling, assay characteristics, and reference standard [13]. Some studies have also shown that both the location and type of specimen collection site can affect the accuracy of this test. Furthermore, the absence of a practical gold standard for the diagnosis of COVID-19 complicates the assessment of the diagnostic accuracy of the test [13].

According to World Health Organization (WHO) diagnostic guidance, detection of SARS-CoV-2 RNA by a validated nucleic acid amplification test supports laboratory confirmation of SARS-CoV-2 infection; repeat testing may be considered when clinical suspicion remains high despite an initial negative result [14]. Therefore, identifying the clinical characteristics associated with an increased likelihood of a positive RT-PCR result among patients suspected of COVID-19 may help clinicians prioritize repeat testing, improve screening strategies, and facilitate timely clinical management. Besides laboratory testing, imaging techniques such as chest radiography [15] and high-resolution computed tomography (HRCT) [16] can assess pulmonary abnormalities, but imaging alone does not establish SARS-CoV-2 infection. Over the course of the pandemic, numerous studies have developed prognostic models and identified clinical characteristics associated with COVID-19 severity and mortality, highlighting the importance of early risk stratification in clinical practice [17, 18].

Previous studies have identified several epidemiological and clinical characteristics associated with SARS-CoV-2 infection, including elevated body temperature, gastrointestinal symptoms, and increased respiratory rate [3, 19]. While numerous studies have developed prediction models for either SARS-CoV-2 diagnosis or COVID-19 prognosis using conventional statistical approaches [17, 18], relatively few studies have jointly assessed factors associated with RT-PCR positivity among hospitalized patients with suspected COVID-19 and explored nonlinear interactions associated with mortality among laboratory-confirmed patients within the same cohort. By combining Least Absolute Shrinkage and Selection Operator (LASSO) regression for parsimonious variable selection with Multifactor Dimensionality Reduction (MDR) for exploring higher-order interactions, the present study provides two complementary descriptive analyses, variable selection for RT-PCR positivity and interaction exploration for mortality, rather than a single unified prediction framework. Therefore, this study aimed to explore clinical characteristics associated with a positive RT-PCR result among patients suspected of COVID-19 and factors associated with in-hospital mortality among patients with confirmed COVID-19 admitted to Ali-Ibn Abi-Talib Hospital in Rafsanjan, Iran.

MATERIAL AND METHODS

Study design and participants. This retrospective observational study was conducted at the sole referral hospital in Rafsanjan, located in the north of Kerman Province, Iran. The source population comprised 544 patients with suspected or confirmed COVID-19 admitted to Ali-Ibn Abi-Talib Hospital, Rafsanjan, during April–July 2022. All consecutive eligible admissions during the study period were included, and data were extracted from hospital medical records. The inclusion criterion was hospitalization with suspected or confirmed COVID-19, as operationally defined below. Suspected COVID-19 was defined, according to the Iranian Ministry of Health and Medical Education national diagnostic guideline applicable during the study period, as the presence of compatible clinical symptoms and/or radiological findings suggestive of COVID-19 pneumonia for which RT-PCR testing was requested at admission. Laboratory-confirmed cases were defined as patients with a positive SARS-CoV-2 RT-PCR result. Patients with missing RT-PCR results, final hospital outcomes, or pre-specified demographic or clinical variables required for the primary analyses were excluded from the analytic cohort. Of the 544 patients in the initial cohort, 39 (7.2%) were excluded because of missing pre-specified analytic variables. This study was approved by the Ethics Committee of Rafsanjan University of Medical Sciences (approval No. IR.RUMS.REC.1399.160, dated October 2020). The requirement for individual informed

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consent was waived by the Ethics Committee because of the retrospective design and use of de-identified records.

Data collection. A structured data-extraction form was used to collect data from patients' medical records. The checklist included the following variables: demographic characteristics (age, sex); clinical presentation (fever, cough, myalgia, dyspnea); ancillary diagnostic findings (chest HRCT findings and peripheral oxygen saturation (SpO_2)); underlying conditions (cancer, chronic liver disease, diabetes mellitus, chronic hematologic disease, immunodeficiency, pregnancy, cardiovascular disease, chronic kidney disease, asthma, chronic neurological disease, hypertension); recorded ward category (general ward, isolation ward, or ICU); intubation status; and final outcome (death or recovery). Positive HRCT was defined as imaging findings compatible with COVID-19 pneumonia, including bilateral ground-glass opacities, multifocal patchy consolidations, or a combination of these findings [20]. $SpO_2 < 93\%$ on ambient air was recorded based on the pre-specified admission measurement obtained by pulse oximetry at hospital admission. Patients were admitted to one of three distinct wards based on clinical severity and physician discretion. The precise time point used to define ward category relative to RT-PCR sampling and subsequent transfers was not documented; ward category was therefore treated as a care-process characteristic, not a validated baseline predictor. To ensure data quality and consistency, the checklist was pilot-tested on 10 randomly selected medical records prior to data collection. Two trained researchers independently extracted the data, and any discrepancies were resolved through discussion and consensus under the supervision of a senior investigator. Formal inter-rater reliability statistics (*e.g.,* Cohen's κ) were not calculated.

Although a WHO-based severity definition (which can include respiratory rate ≥ 30 breaths/min, $SpO_2 < 90\%$, or other signs of severe respiratory compromise) was considered [21], it was not used in the primary models because it overlapped with the ward, intubation, and hypoxemia variables.

Statistical analysis. Quantitative variables were summarized as mean ± standard deviation (SD), whereas qualitative variables were presented as frequencies and percentages. Associations between individual clinical characteristics and RT-PCR status (positive *vs.* negative) were initially assessed using univariable logistic regression. Continuous variables, including age, were modeled as continuous predictors without categorization. To perform penalized variable selection and reduce model complexity, LASSO logistic regression was applied using the cv.glmnet function in the glmnet package in R [22, 23]. The optimal value of the regularization parameter (λ) was selected by 10-fold cross-validation using the λ value that minimized the mean cross-validated binomial deviance (λ.min). Variables with non-zero LASSO coefficients were subsequently entered into an unpenalized logistic regression model; the resulting confidence intervals and *P*-values do not account for the preceding data-driven selection and should be viewed as descriptive. Because of the retrospective observational design, associations are not interpreted as causal or strictly temporal predictors. Intubation was included in the reported full-cohort association model despite its potentially post-admission occurrence; this model therefore cannot be interpreted as a purely baseline diagnostic prediction model. The apparent discriminative performance of the refitted multivariable model was assessed using the receiver operating characteristic (ROC) curve and the corresponding area under the curve (AUC).

Factors associated with mortality among patients with confirmed COVID-19 were explored using MDR analysis to describe single-variable prediction and pairwise differences in balanced accuracy among candidate predictors [24]. MDR was used descriptively because the number of deaths (n = 30) was small relative to the number of candidate variables; no adjusted effect estimates or formal inference were derived from MDR. Hierarchical dendrograms and circular network graphs were used to visualize exploratory pairwise differences in cross-validated balanced accuracy. MDR computations were conducted with the scikit-mdr package using 10-fold cross-validation. Other statistical analyses used SPSS version 19 (IBM Corp., Armonk, NY, USA) and R version 3.6.3 with glmnet. For the logistic regression analyses, a two-sided *P*-value < 0.05 was considered statistically significant. MDR analyses were exploratory; comparisons across 153 candidate pairs were not supported by confirmatory hypothesis tests or external validation.

RESULTS

Study population and baseline characteristics. Of 544 hospitalized patients, 505 were included in the analytic cohort, of whom 51.3% (n = 259) were RT-PCR-positive and 48.7% (n = 246) were RT-PCR-negative. The overall mean age was 54.7 ± 20.4 years: 53.6 ± 19.4 years in RT-PCR-positive patients and 55.6 ± 21.7 years in RT-PCR-negative patients. The proportion of male patients was 52.3% (n = 264) overall, including 50.2% (n = 130) of RT-PCR-positive patients and 54.5% (n = 134) of RT-PCR-negative patients. No statistically significant differences were observed between the RT-PCR-positive and RT-PCR-negative groups in age (*P* = 0.27) or sex (*P* = 0.336). The remaining demographic and clinical characteristics of the two groups are presented in Table 1.

Factors associated with RT-PCR positivity. After LASSO-based variable selection, cough, dyspnea, myalgia, cardiovascular disease, diabetes mellitus, hypertension, ward of admission, intubation, and chronic kidney disease had non-zero coefficients and were subsequently entered into an unpenalized multivariable logistic regression model for coefficient estimation and statistical inference (n = 505).

In the unpenalized model refitted after LASSO selection, cough (OR = 1.66, 95% CI: 1.13–2.44), myalgia (OR = 1.60, 95% CI: 1.08–2.38), and hypertension (OR = 1.90, 95% CI: 1.05–3.51) were associated with higher odds of RT-PCR positivity, whereas cardiovascular disease (OR = 0.42, 95% CI: 0.21–0.84) was associated with lower odds (Table 2). Compared with admission to the isolation ward (reference category), admission to the general ward (OR = 0.40, 95% CI: 0.24–0.65) or to the ICU (OR = 0.26, 95% CI: 0.13–0.50) was associated with lower odds of RT-PCR positivity. Intubation was also associated with higher odds of RT-PCR positivity (Or = 2.94, 95% CI: 1.141-6.33), and

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is reported as a post-admission severity marker rather than a baseline predictor because it may have occurred after admission and after RT-PCR-informed care. Although dyspnea, diabetes mellitus, and chronic kidney disease were selected by the LASSO procedure, their refitted estimates did not meet the nominal $P < 0.05$ threshold (diabetes mellitus, $P = 0.44$; dyspnea, $P = 0.35$; and chronic kidney disease, which approached statistical significance, $P = 0.054$). The apparent AUC of the refitted model was 0.691 (95% CI: 0.646–0.737).

Because age is a well-established determinant of both the clinical presentation and the severity of COVID-19, and because the factors associated with RT-PCR positivity may differ between older and younger patients, a pre-specified subgroup analysis stratified by age (elderly, ≥ 60 years, n = 211; non-elderly, < 60 years, n = 294) was performed, applying the same LASSO variable-selection and refitting procedure independently within each subgroup.

Table 1. Baseline characteristics of patients stratified by RT-PCR result

Characteristic	RT-PCR$^+$ (n=259)	RT-PCR$^-$ (n=246)	Test statistic	*P*-value
Male sex, n (%)	130 (50.2)	134 (54.5)	0.926[a]	0.336
Age, years, mean ± SD	53.6 ± 19.4	55.6 ± 21.7	−1.150[c]	0.270
Ward of admission, n (%)[e]			28.562[a,e]	< 0.001[e]
General ward	37 (14.3)	67 (27.2)		
ICU	28 (10.8)	51 (20.7)		
Isolation ward	194 (74.9)	128 (52.0)		
Clinical presentation and admission status, n (%)				
Fever	160 (61.8)	135 (54.9)	2.471[a]	0.116
Cough	118 (45.6)	80 (32.5)	9.000[a]	0.003
Myalgia	128 (49.4)	98 (39.8)	4.687[a]	0.030
Dyspnea	114 (44.0)	99 (40.2)	0.736[a]	0.391
Intubation	29 (11.2)	26 (10.6)	0.051[a]	0.821
SpO_2 < 93%	146 (56.4)	149 (60.6)	0.916[a]	0.339
Any underlying condition, n (%)	110 (42.5)	113 (45.9)	0.614[a]	0.433
Specific underlying conditions, n (%)				
Hypertension	52 (20.1)	33 (13.4)	4.000[a]	0.045
Diabetes mellitus	43 (16.6)	26 (10.6)	3.893[a]	0.048
Cardiovascular disease	18 (6.9)	29 (11.8)	3.500[a]	0.061
Other chronic respiratory disease[d]	15 (5.8)	38 (15.4)	12.522[a]	< 0.001
Chronic kidney disease	3 (1.2)	8 (3.3)	—[b]	0.133
Chronic neurological disorder	7 (2.7)	8 (3.3)	0.132[a]	0.726
Asthma	2 (0.8)	2 (0.8)	—[b]	1.000
Cancer	6 (2.3)	10 (4.1)	1.257[a]	0.262
Chronic hematologic disease	9 (3.5)	9 (3.7)	0.012[a]	0.911
Chronic liver disease	1 (0.4)	1 (0.4)	—[b]	1.000
Immunodeficiency	1 (0.4)	1 (0.4)	—[b]	1.000
Pregnancy among female patients, n (%)[f]	2 (1.6)	4 (3.6)	—[b]	0.421
Clinical outcome, n (%)[e]			1.311[a, e]	0.252[e]
Death	30 (11.6)	37 (15.0)		
Recovery	229 (88.4)	209 (85.0)		

[a] Pearson chi-square test without continuity correction; [b] two-sided Fisher's exact test (no chi-square test statistic); [c] independent-samples t-test. [d] Chronic respiratory disease other than asthma. [e] Ward of admission (3×2 contingency table: General ward vs. ICU vs. Isolation ward) and Clinical outcome (2×2 contingency table: Death *vs*. Recovery) each consist of mutually exclusive categories summing to 100% within each group; therefore, a single overall (omnibus) Pearson chi-square test statistic and *P*-value are reported for the entire variable rather than separate *P*-values for each category row. [f] Percentages are calculated among female patients (n=129 in the RT-PCR$^+$ group and n=112 in the RT-PCR$^-$ group).

Table 2. Adjusted odds ratios for candidate clinical characteristics associated with RT-PCR positivity in refitted multivariable logistic regression models

Clinical characteristic	Non-elderly (n = 294): Adjusted OR (95% CI), *P*	Elderly (n = 211): Adjusted OR (95% CI), *P*	All patients (n = 505): Adjusted OR (95% CI), *P*
Cough	1.58 (0.97–2.58), 0.071	1.61 (0.81–3.23), 0.190	1.66 (1.13–2.44), 0.010
Dyspnea	—	2.64 (1.29–5.59), 0.008	1.21 (0.82–1.81), 0.350
Myalgia	1.40 (0.87–2.28), 0.160	1.28 (0.62–2.69), 0.490	1.60 (1.08–2.38), 0.020
Cardiovascular disease	—	0.42 (0.16–1.10), 0.079	0.42 (0.21–0.84), 0.014
Diabetes mellitus	—	—	1.27 (0.69–2.39), 0.440
Hypertension	—	4.42 (1.97–10.60), <0.001	1.90 (1.05–3.51), 0.034
General ward *vs.* isolation	0.56 (0.33–0.96), 0.036	—[a]	0.40 (0.24–0.65), <0.001
ICU *vs.* isolation	0.19 (0.05–0.57), 0.004	0.17 (0.06–0.47), 0.001	0.26 (0.13–0.50), <0.001
Intubation	—	15.00 (4.52–58.10), <0.001	2.94 (1.41–6.33), 0.005
Chronic neurological disease	—	0.21 (0.04–0.98), 0.047	—
Chronic kidney disease	—	0.11 (0.01–0.63), 0.021	0.24 (0.05–1.03), 0.054

Note: Adjusted ORs, CIs, and *P*-values are from unpenalized multivariable logistic regression models refitted after LASSO variable selection. Variables eliminated by LASSO in all three models (fever, SpO_2 < 93%, positive HRCT, chronic hematologic disease, asthma, immunodeficiency, pregnancy, chronic liver disease, and cancer) are not shown. A dash (—) indicates that the variable was not retained following LASSO selection or, for the general-ward category in older patients, that the ordinary maximum-likelihood estimate was not reliably estimable because of quasi-complete separation. Intubation is a potentially post-admission severity marker and should not be used for baseline diagnostic prediction. Nominal *P*-values and confidence intervals do not adjust for selection by LASSO. Variable definitions are provided in Table 1.

[a] Not reliably estimable in the ordinary unpenalized maximum-likelihood model because of quasi-complete separation (only 1 of 26 elderly patients admitted to the general ward was RT-PCR-positive); as described in the text, a separate Firth penalized-likelihood analysis yielded OR = 0.08 (95% CI: 0.01–0.45, $P = 0.004$).

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In the elderly subgroup, dyspnea (OR = 2.64, 95% CI: 1.29–5.59), hypertension (OR = 4.42, 95% CI: 1.97–10.60), and intubation (OR = 15.00, 95% CI: 4.52–58.10) were associated with higher odds of RT-PCR positivity; admission to the ICU (*vs.* the isolation ward; OR = 0.17, 95% CI: 0.06–0.47) was associated with lower odds, whereas chronic neurological disease (OR = 0.21, 95% CI: 0.04–0.98) and chronic kidney disease (OR = 0.11, 95% CI: 0.01–0.63) were associated with lower odds of RT-PCR positivity (Table 2). The wide confidence interval for intubation reflects the small number of intubated patients in this subgroup (n = 34). Admission to the general ward exhibited quasi-complete separation (1 of 26 patients was RT-PCR-positive); a separate Firth penalized-likelihood analysis was reported for this sparse category (OR = 0.08, 95% CI: 0.01–0.45, $P = 0.004$); these estimates are not from the unpenalized model shown in Table 2. The apparent AUC of the elderly-subgroup model was 0.831 (95% CI: 0.777–0.885).

In the non-elderly subgroup, admission to the general ward (OR = 0.56, 95% CI: 0.33–0.96) or the ICU (OR = 0.19, 95% CI: 0.05–0.57), both compared with the isolation ward, was associated with lower odds of RT-PCR positivity, whereas cough approached but did not reach statistical significance (OR = 1.58, 95% CI: 0.97–2.58) (Table 2). The apparent AUC of the non-elderly-subgroup model was 0.630 (95% CI: 0.567–0.693).

Pairwise interactions and synergy. The hierarchical dendrogram (Figure 1) showed seven first-order branch joins. Six pairs had an apparent cross-validated accuracy gain relative to the better single variable: the combination of age ≥ 60 years and cough showed the largest relative gain in testing balanced accuracy among 153 evaluated pairs (testing balanced accuracy = 54.9%, +11.1 percentage points over the better-performing single variable), followed by sex combined with diabetes mellitus (59.6%, +5.0 percentage points), general ward combined with chronic hematologic disease (58.8%, +3.7 percentage points), intubation combined with cancer (58.4%, +3.5 percentage points), dyspnea combined with other chronic respiratory disease (56.3%, +4.0 percentage points), and myalgia combined with cardiovascular disease (+0.9 percentage points). Hypertension and positive HRCT findings formed the only directly joined pair without an apparent gain, with the joint model providing no improvement over hypertension alone (both 57.6%). Additionally, although not directly joined as a first-order pair in the hierarchical dendrogram, the combination of intubation and $SpO_2 < 93\%$ showed a descriptive gain in pairwise accuracy in the pairwise network analysis (Figure 2), consistent with their shared reflection of advanced respiratory failure.

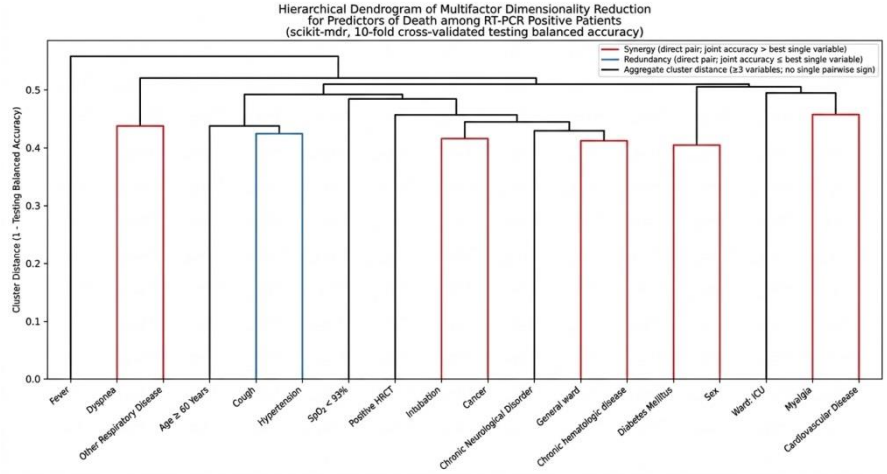


Fig. 1. Hierarchical dendrogram from the Multifactor Dimensionality Reduction analysis (scikit-mdr in Python, 10-fold cross-validated testing balanced accuracy) of candidate factors associated with mortality among RT-PCR-positive patients. The y-axis is cluster distance, calculated as 1 minus the testing balanced accuracy of the joint (or aggregate) model; a shorter distance indicates a variable combination with higher cross-validated predictive accuracy for mortality. Only branches joining exactly two original variables directly (first-order merges) are colored: red indicates an apparent positive balanced-accuracy difference for a joined pair; blue indicates no positive difference. Such cross-validated classification differences do not by themselves establish statistically significant interactions. Black branches join clusters of three or more variables via average-linkage distance and therefore do not correspond to a single pairwise interaction sign. Abbreviations: DM, diabetes mellitus; HTN, hypertension; HRCT, high-resolution computed tomography; SpO_2, peripheral oxygen saturation. Other chronic respiratory disease refers to a chronic respiratory condition other than asthma (defined in Table 1).

Single-variable predictive accuracy and overall model performance. Considered individually, hypertension had the highest single-variable testing balanced accuracy for mortality (57.6%), followed by $SpO_2 < 93\%$ (55.2%), general ward (55.1%), intubation (55.0%), and sex (54.6%); single-variable balanced accuracies ranged from 37.4% to 57.6%, including values below the 50% chance benchmark; the modest number of deaths (n = 30) raises concerns about instability, but the reason for subchance estimates cannot be established without cross-validation predictions. Of the 153

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evaluated pairs, 28 (18.3%) showed a positive descriptive gain over the stronger single variable and 125 (81.7%) did not. The pairs with the largest negative differences were cough combined with cardiovascular disease (−17.4 percentage points relative to the better single variable), dyspnea combined with myalgia (−16.1 percentage points), and cough combined with sex (−14.5 percentage points); the pairs with the largest positive differences were age ≥ 60 years combined with cough (+11.1 percentage points) and diabetes mellitus combined with age ≥ 60 years (+9.6 percentage points). Overall, single-variable and pairwise testing balanced accuracies ranged from 37.4% to 59.6%, indicating that none of the candidate predictors, individually or in combination, provided strong or clinically reliable discrimination of mortality in this cohort. Thus, the MDR analysis did not identify a clinically useful mortality prediction model (Figures 1 and 2).

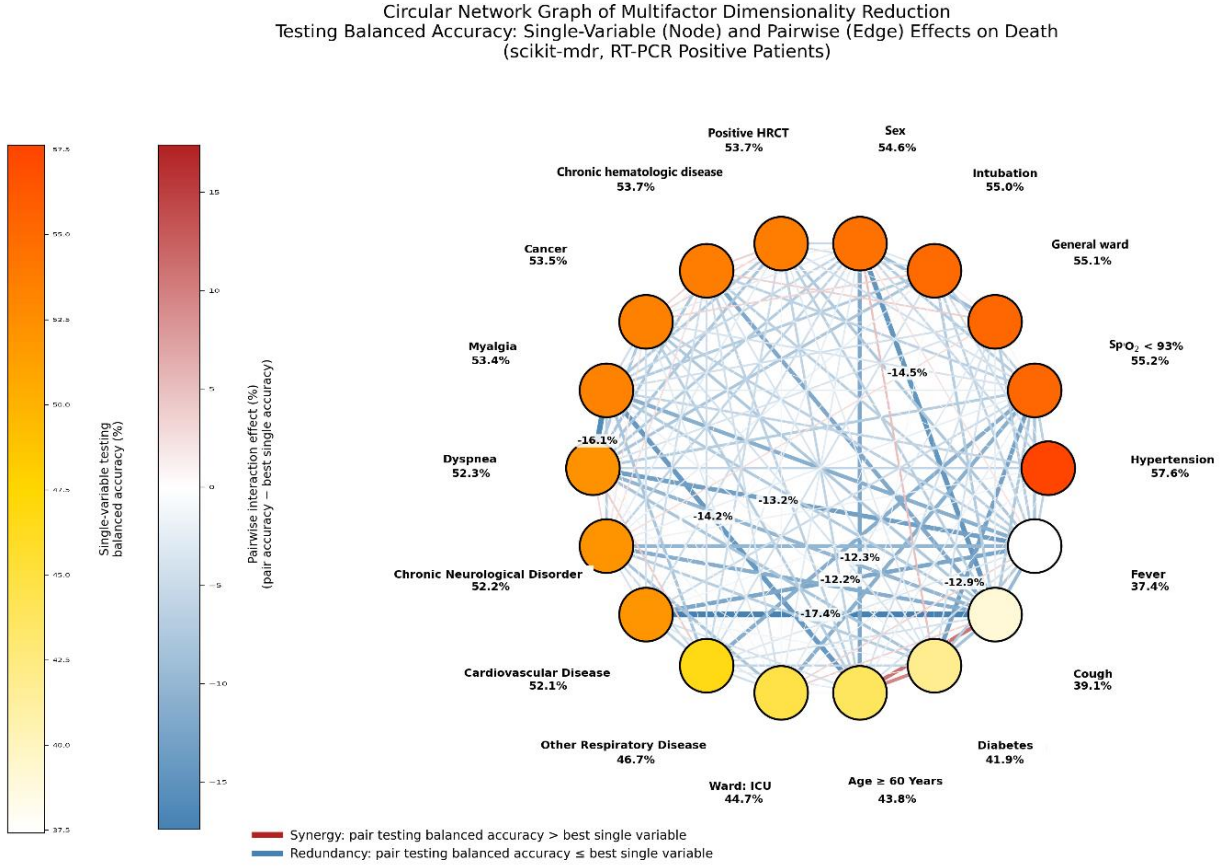


Fig. 2. Circular network graph of Multifactor Dimensionality Reduction analysis: single-variable and pairwise-interaction testing balanced accuracy for mortality among RT-PCR-positive patients.

Analysis was performed using the Multifactor Dimensionality Reduction algorithm (scikit-mdr package in Python) with 10-fold cross-validated testing balanced accuracy, on 18 candidate predictors. The composite "Any underlying condition" variable was excluded due to overlap with individual comorbidities, and conditions with cell counts ≤ 2 (asthma, chronic liver disease, immunodeficiency, and pregnancy) were excluded due to data sparsity. Each node represents one predictor variable; the percentage beside it is that variable's single-variable testing balanced accuracy for mortality, and node color intensity scales continuously with this value (see left color bar; darker orange/red = higher accuracy). Connecting lines represent the pairwise interaction effect between two variables, defined as the pairwise (two-variable) testing balanced accuracy minus the higher of the two corresponding single-variable accuracies; line color indicates the sign and magnitude of this effect on a continuous scale (see right color bar): red denotes a positive descriptive difference and blue denotes a zero or negative difference relative to the better single variable; these differences do not establish biological or statistical interactions. Line thickness is proportional to the magnitude of the interaction effect. For clarity, numeric labels are shown only for the eight strongest pairwise interactions.

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DISCUSSION

RT-PCR is widely used for the detection of SARS-CoV-2, ranging from screening asymptomatic individuals to the diagnosis of symptomatic infections. Although false-negative RT-PCR results may occur during the early stages of infection or due to sampling-related factors, repeated testing is recommended when clinical suspicion remains high [25]. Notably, this study was conducted between April and July 2022, a period during which Omicron sublineages were widely circulating and population vaccination coverage had increased compared with the early pandemic [11, 26]. Given that Omicron-era infections are generally associated with a milder clinical course and lower mortality than infections with earlier variants, and that vaccination further attenuates disease severity, the symptom profile, comorbidity associations, and in-hospital mortality reported here should be interpreted as observed during the Omicron era; individual vaccination and viral sequencing data were not available for confirmation and may not be directly generalizable to cohorts studied earlier in the pandemic.

In the present study, LASSO variable selection followed by an unpenalized multivariable logistic regression model identified cough, myalgia, hypertension, cardiovascular disease, ward of admission, and intubation as variables associated with RT-PCR positivity in the post-selection model among hospitalized patients with suspected COVID-19. The association with admission to the isolation ward should be interpreted with caution, as ward assignment was primarily determined by clinical suspicion and infection-control policies rather than as an independent clinical characteristic, introducing the possibility of incorporation bias. Intubation was not interpreted as a temporal predictor because it typically occurs after disease progression and RT-PCR-informed management. Furthermore, age-stratified analyses demonstrated that these associations varied by age group. In elderly patients, dyspnea, hypertension, and intubation (a post-admission severity marker) were the variables most strongly associated with RT-PCR positivity, whereas in non-elderly patients, ward of admission remained the main discriminator. These findings suggest that the clinical presentation associated with RT-PCR positivity is not uniform across age groups and that age-specific assessment strategies may improve clinical evaluation.

Clinically, the presence of cough and myalgia in the overall cohort, and of dyspnea and hypertension in elderly patients, may help identify hospitalized patients with suspected COVID-19 who warrant closer monitoring and consideration for repeat RT-PCR testing. However, given the moderate discriminative performance of the predictive models and the lack of external validation, these variables should be considered adjuncts to clinical judgment rather than components of a validated decision-support tool.

Our findings are generally consistent with previous reports showing that respiratory and systemic symptoms are among the most informative clinical indicators of SARS-CoV-2 infection. In a meta-analysis of data from 1,994 patients, the most common clinical manifestations were fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), and dyspnea (21.9%) [27]. Similarly, Wan *et al*. reported fever, cough, and fatigue as the predominant presenting symptoms among patients with laboratory-confirmed COVID-19 [28]. Talebi *et al*. also found dyspnea, cough, and fever to be the most frequent manifestations in hospitalized patients [29]. Notably, all three of these studies were conducted during the early pandemic period, prior to the availability of vaccines, whereas our cohort was recruited during the Omicron-dominant period of higher vaccination coverage; differences in symptom prevalence between our findings and these studies may therefore partly reflect this temporal and immunological context rather than methodological differences alone.

Unlike these descriptive studies, our analysis used LASSO variable selection followed by refitting in an unpenalized multivariable logistic regression model to identify independently associated variables while simultaneously accounting for multiple demographic and clinical variables. In our multivariable analysis, cough and myalgia remained independently associated with RT-PCR positivity, whereas fever did not retain independent predictive value. This finding suggests that although fever is highly prevalent among patients with COVID-19, its ability to distinguish RT-PCR-positive from RT-PCR-negative hospitalized patients with suspected SARS-CoV-2 may diminish after adjustment for other correlated clinical features. Likewise, dyspnea demonstrated an age-dependent association, remaining independently associated only in elderly patients. Given that dyspnea typically develops several days after symptom onset [28], this age-specific effect may reflect differences in disease severity and timing of hospital presentation between younger and older patients. Hypertension and cardiovascular disease emerged as comorbidities associated with RT-PCR positivity, hypertension with higher odds and cardiovascular disease with lower odds, whereas diabetes mellitus and chronic kidney disease were not independently associated in the multivariable model.

Norooznezhad *et al*. reported that age, cardiovascular disease, diabetes mellitus, chronic lung disease, and ICU admission were significantly associated with RT-PCR-confirmed COVID-19 [30]. Likewise, Gholampour *et al*. observed that older age and underlying conditions, particularly diabetes mellitus and chronic obstructive pulmonary disease, were common among hospitalized

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COVID-19 patients [31]. Richardson *et al*. also demonstrated that most hospitalized patients had at least one chronic comorbidity, with hypertension and diabetes mellitus being the most prevalent conditions [32]. Notably, these studies largely predate the Omicron era and widespread vaccination, which may further explain why a narrower range of comorbidities retained independent predictive value in our more recent cohort.

Although these studies consistently highlight the importance of underlying conditions in hospitalized patients with COVID-19, most relied on descriptive or conventional regression analyses. In contrast, our study applied LASSO regression followed by refitting in an unpenalized model, which simultaneously accounts for multiple correlated variables and retains only those providing independent predictive information. Under this more stringent approach, hypertension remained independently associated and cardiovascular disease was inversely associated, whereas diabetes mellitus and chronic kidney disease were not. This difference underscores the importance of penalized variable-selection methods in distinguishing conditional associations from factors that are merely associated because of shared relationships with age, disease severity, or other clinical characteristics.

The strong association between hypertension and RT-PCR positivity observed in our study is also biologically plausible. Hypertension has been linked to endothelial dysfunction, chronic inflammation, and alterations in the renin–angiotensin system, all of which may influence host susceptibility and disease expression following SARS-CoV-2 infection [33]. The inverse association with cardiovascular disease should not be interpreted causally; it may reflect confounding by indication, survivor bias, medication effects, competing diagnoses, or sparse data. Nevertheless, because the present study included only hospitalized patients with clinically suspected COVID-19, these findings should be interpreted as factors associated with RT-PCR positivity within this specific clinical setting rather than risk factors for acquiring SARS-CoV-2 infection in the general population.

The present study also explored factors associated with in-hospital mortality among patients with confirmed COVID-19 using MDR, a machine-learning approach designed to identify both individual predictor effects and higher-order interactions. Unlike conventional regression methods, MDR evaluates how combinations of clinical characteristics jointly contribute to the outcome rather than considering each predictor independently. In this dataset, some two-variable combinations showed small gains in cross-validated balanced accuracy over their better constituent variable, without establishing genuine statistical interactions or clinically useful prediction.

The hierarchical dendrogram identified the combination of intubation and cancer as one of the pairs with a larger observed increase in balanced accuracy (testing balanced accuracy = 58.4%), together with the combination of age ≥ 60 years and cough, which had the largest relative gain in balanced accuracy among all evaluated pairs (54.9%, an improvement of 11.1 percentage points over either variable alone). A separate pair with an apparent cross-validated accuracy gain, intubation combined with SpO_2 < 93%, was also identified in the pairwise network analysis, consistent with the fact that both variables reflect advanced respiratory failure. A study of hospitalized COVID-19 patients with neurological disorders reported lower oxygen saturation in association with mortality and intubation; it did not establish these variables as independent predictors of mortality [34]. Clinically, this association is expected, as their coexistence likely represents a stage of disease associated with markedly increased mortality risk. Additional synergistic interactions were observed between sex and diabetes mellitus, between admission to the general ward and chronic hematologic disease, and between dyspnea and other chronic respiratory disease, but these exploratory accuracy differences require independent replication and do not, by themselves, support clinical mortality prediction. Notably, age ≥ 60 years alone had a testing balanced accuracy of only 43.8%, below the 50% chance level, and its predictive value emerged only in combination with other variables (particularly cough), but this result should not be interpreted as proving that age is unimportant for mortality risk. However, the best-performing pair in absolute terms reached only a testing balanced accuracy of 59.6%, which is close to the chance level and not clinically reliable.

The single-variable testing balanced accuracy analysis further demonstrated that hypertension had the greatest individual contribution to mortality prediction (57.6%), followed by SpO_2 < 93% (55.2%), admission to the general ward (55.1%), intubation (55.0%), and sex (54.6%). Although the individual effects of these variables were modest, and all single-variable and pairwise testing balanced accuracies in this analysis ranged from 37.4% to 59.6%, close to the chance level, the strongest pairwise classifications remained only marginally more accurate than single-variable classifications (up to 59.6% for sex combined with diabetes mellitus). These exploratory results cannot establish the relative causal contributions of the candidate factors to mortality. Although the overall predictive accuracy achieved, whether by single variables or by their combinations, remained too close to the chance level to support confident individual-patient risk prediction, these mortality-related findings should accordingly be regarded as exploratory and hypothesis-generating.

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In the present study, the in-hospital mortality proportion among patients with confirmed COVID-19 was 11.6% (30 of 259 RT-PCR-positive patients). Talebi *et al.* reported an in-hospital mortality rate of approximately 14%, with most fatal cases occurring in patients with underlying conditions [29]. In contrast, Zhou *et al.* reported higher early-pandemic in-hospital mortality (54 deaths among 191 patients, 28.3%) among selected hospitalized patients [35], whereas Omicron-era comparative studies have generally reported lower risks of severe outcomes [11, 36], and reported mortality varies substantially across hospitalized cohorts and periods [26]. These differences likely reflect variations in study populations, age distributions, baseline comorbidity profiles, disease severity at admission, healthcare capacity, and the pandemic period. Early reports from the first pandemic waves generally included more critically ill patients from unvaccinated populations, whereas later cohorts, including our own, conducted during the Omicron-dominant period in 2022, may have benefited from earlier diagnosis, improved supportive care, evolving therapeutic strategies, and the inherently milder clinical course associated with Omicron infection and vaccination [26]. Consistent with these observations, Goodarzi *et al.* reported that although a substantial proportion of patients who died had no documented underlying condition, diabetes mellitus, hypertension, and malignancy were the most frequent comorbidities [37]. Despite differences in reported mortality rates, the available evidence consistently indicates that severe respiratory compromise and underlying chronic conditions are major determinants of adverse outcomes [38]. Our exploratory MDR analysis found that certain pairwise combinations, particularly age $\geq$ 60 years with cough and intubation with cancer or SpO_2 < 93%, provided marginally greater predictive information than any single variable alone, although absolute discrimination remained modest. These findings underscore that mortality risk assessment in hospitalized patients with COVID-19 should integrate multiple concurrent clinical features rather than rely on isolated predictors; however, validation in larger, independent cohorts is required before such an approach can inform prospective clinical decision-making.

This study has several limitations that should be considered when interpreting the findings. First, because of its retrospective design, some medical records were excluded due to incomplete information, which may have introduced selection bias. The characteristics of excluded patients were not systematically reported or compared with those of included patients. Second, the study population consisted exclusively of hospitalized patients from a single referral hospital; therefore, the findings may not be generalizable to outpatients, patients with milder disease, or populations with different demographic and clinical characteristics.

Third, patients with negative RT-PCR results were included as suspected COVID-19 cases based on clinical manifestations and HRCT findings according to the national diagnostic protocol used during the study period. Consequently, the RT-PCR-negative group remained clinically similar to the confirmed group, which may have introduced selection and diagnostic-classification bias when evaluating factors associated with RT-PCR positivity. Therefore, the identified associations should be interpreted within the context of hospitalized patients with a high clinical suspicion of COVID-19 rather than as diagnostic predictors applicable to the general population.

Fourth, intubation and ward of admission introduce temporal ambiguity and possible incorporation bias; intubation should not be interpreted as a baseline predictor of RT-PCR positivity. Fifth, the mortality analysis based on MDR should be considered exploratory. The number of deaths (n = 30) was small relative to the number of candidate variables, and cross-validated balanced accuracies were generally close to the 50% chance level; repeated screening of 153 pairs without an independent test set can exaggerate apparent improvements. Although MDR is useful for identifying complex interactions among predictors, the observed interaction patterns require confirmation in larger independent cohorts using complementary analytical approaches.

Sixth, although LASSO selection used internal cross-validation, the reported AUCs were apparent (in-sample) estimates and no independent validation dataset was available to evaluate their reproducibility or generalizability. Therefore, the predictive performance of the refitted model should be confirmed in future multicenter studies before clinical implementation. Seventh, the structured data-extraction form was pilot-tested, but formal inter-rater reliability statistics were not calculated. Eighth, severity categories were not separately modeled because they overlapped with other recorded indicators. Ninth, vaccination status, variant confirmation, specimen sampling details, and timing of intubation relative to RT-PCR were not documented in the available analytical report.

In conclusion, despite these limitations, the present study included all consecutive eligible hospitalized admissions during the study period at the sole referral hospital in Rafsanjan. In addition, the use of LASSO regression for variable selection and MDR for exploring higher-order interactions provided descriptive, hypothesis-generating insights into factors associated with RT-PCR positivity and in-hospital mortality, which may serve as a foundation for future validation studies.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest associated with this manuscript.

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DATA AVAILABILITY

The data that support the findings of this study were obtained from patients' medical records. Due to the sensitive nature of patient health information and privacy restrictions imposed by the Ethics Committee of Rafsanjan University of Medical Sciences, the data are not publicly available. However, de-identified data may be made available from the corresponding author upon reasonable request, subject to institutional review and approval.

AI DISCLOSURE

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the writing, editing, or preparation of this manuscript.

AUTHORS' CONTRIBUTIONS

GB: Conceptualization, Data curation, Supervision; FA: Data curation; FB: Investigation, Supervision; ZM: Formal analysis; ZK: Conceptualization, Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing. All authors read and approved the final manuscript.

ETHICS STATEMENT

The study was approved by the Ethics Committee of Rafsanjan University of Medical Sciences in October 2020 (Approval No. IR.RUMS.REC.1399.160). The approval covered retrospective use of de-identified medical records for COVID-19 research. Because of the retrospective design of the study and the use of anonymized (de-identified) medical records, the requirement for obtaining written informed consent from individual patients was reportedly waived by the Ethics Committee. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. Patient confidentiality was strictly maintained throughout the study.

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