Unveiling the hidden effect of multi-morbidities on the severity of Covid-19: a latent class analysis approach

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Abstract

Background Epidemiological studies showed that Covid-19 patients with underlying diseases had higher rates of severe Covid-19. Previous studies focused on the presence of a single chronic disease but this study investigated the prevalence and patterns of multi-morbidities in patients with Covid-19 and its relationship with the severity of Covid-19.

Methods This retrospective study focused on patients age 30 years and older with positive polymerase chain reaction (PCR) results in 24 hospitals of Mashhad in northeastern Iran from 20-3-2020 to 21-1-2022. The number of studied confirmed patients was 318,502. The underlying diseases were identified according to the International Classification of Diseases, and the severity of Covid-19, including death, need for ventilation, and need for treatment in the intensive care unit (ICU). The pattern of multi-morbidities in these confirmed cases was investigated using latent class analysis (LCA), and the relationship between this pattern and the severity of Covid-19 was determined by multivariate logistic regression.

Results The most common coexisting diseases were hypertension in 30,100 patients (9.5%), metabolic disorders in 23,798 (7.5%) and hyperlipidemia in 22,454 (7%). Different comorbidities were grouped into three classes by the LCA model. Class 1 was patients without multi-morbidities, or 83% people., Class 2, which included 9% patients, was patients with hypertension, diabetes, respiratory diseases, and mental behavioral disorders (HRMD class). Class 3, which included patients with metabolic diseases, for whom the probability of developing hypertension, hyperlipidemia, diabetes, and metabolic disorders was high, included 7% patients. The results of multivariate logistic regression showed that having HRMD and metabolic diseases compared to no multi-morbidity adjusted for some risk factors increased the odds of developing severe Covid-19 by 81% and 55%, respectively.

Conclusions The classes identified in this study provided a clear view of different groups of Covid-19 patients with certain multi-morbidities and underscore the importance of considering these patterns, rather than individual comorbidities, in risk assessment and management of COVID-19 patients. This approach will guide clinical decision-making and resource allocation in the ongoing management of the COVID-19 pandemic.

Keywords Covid-19, Multi-morbidities, Severity, Latent class analysis (LCA)

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Background

As cases of Covid-19 increased rapidly in 2020, the World Health Organization declared that a pandemic existed on March 11, 2020. Measures were taken to control the outbreak and became a top priority in most countries of the world [1]. According to data from the Ministry of Health of Iran and the World Health Organization, as of July 29, 2023, 7,612,886 cases of Covid-19 and 146,307 deaths due to it had been reported in Iran and 692,199,286 cases and 6,903,307 deaths had been reported in the world [2].

Epidemiological studies showed that Covid-19 patients with underlying diseases such as cardiovascular diseases, chronic kidney disease, chronic lung diseases, diabetes, hypertension, immune system deficiencies, and obesity had higher rates of hospitalization, severity of Covid-19, and admissions to intensive care units (ICUs), and that ultimately, they also had higher rates of mortality [3–5]. For example, hypertension and diabetes in Covid-19 patients increased their risk of dying more than twofold and that cardiovascular diseases, chronic lung diseases, and cancer increased their risk of death more than threefold [6, 7]. Elderly people, who are more susceptible to underlying and chronic diseases [8] experienced higher rates of admission to ICUs with Covid-19 and had higher mortality rates from the diseases [4, 9, 10].

Knowledge about patterns of comorbidities provides the necessary information for formulating guidelines for patients with concurrent underlying diseases and can help public authorities to allocate resources effectively and maintain high health standards [11, 12].

Previous studies focused on the presence of a single chronic disease rather than the presence of several diseases at a time which is called multi-morbidity, as is seen in many elderly patients [3–7, 13]. Therefore, this study investigated the prevalence and patterns of multi-morbidities in patients with Covid-19 and its relationship with the severity of Covid-19.

Methods

This retrospective study was conducted in 24 hospitals of Mashhad, located in the northeast of Iran, with the aim of investigating the prevalence and patterns of multi-morbidities in patients with confirmed Covid-19 and the relationship of the multi-morbidities with the severity of Covid-19. The source of the data was the Medical Care Monitoring Center and Sina Electronic Health System (SinaEHR®). This study was approved by the Ethics Council of Shahroud University of Medical Sciences (the ethical cod: IR.SHMU.REC.1401.177).

The number of patients with a positive polymerase chain reaction (PCR) from 20-3-2020 to 21-1-2022 was 405,397. Inclusion criteria included all of patients with a positive PCR who were 30 years of age or older. The number of studied patients was 318,502 who met this criterion. These patients were examined in terms of demographic characteristics such as gender, age, and marital status; vaccination history for Covid-19; history of underlying diseases; and severity of Covid-19, defined by need for ventilation or admission to ICU or death. Patients were divided into two age groups, 30 to 49 years and 50 years and above, and the marital status was coded as single (never married, divorced, deceased spouse) or married. Three vaccination doses were investigated. Underlying diseases were defined and coded using the International Classification of Diseases 10th edition (ICD10) coding system and guidelines. To classify the coexisting diseases, the medical history of all patients was determined. All coexisting diseases were divided into 18 categories based on disease's prevalence and importance by ICD10 coding including: hypertension (I10-15 code), cardiovascular diseases (I0-9, I26-99 code), diabetes and other blood sugar disorders (E10-16 code), hyperlipidemia (E78 code), ischemic heart diseases (I20-25 code), malnutrition (E40-68 code), metabolic disorders (E20-35, E70-90 codes), cancer (C, D0-48 codes), parasitic infectious diseases (A, B codes), neurological system diseases (G code), thyroid diseases (E0-7 code), musculoskeletal diseases (M code), respiratory diseases (J code), digestive diseases (K code), urogenital diseases (N code), mental behavioral diseases (F code), eye and ear diseases (H code), and blood and immune system diseases (D code).

Statistical analysis

Descriptive statistics including the mean and standard deviation (SD) as well as frequency (percentage) were reported for quantitative and qualitative variables. Statistical difference between qualitative variables were evaluated by chi square test. Significant variables in this bivariate analysis were included in the multivariate logistic regression.

After the data had been sorted and entered into the R software, the pattern of multi-morbidities was checked using latent class analysis and the model with the number of different classes of fit and the goodness of fit indices of the model were calculated. All classes of diseases were fitted from class 2 to 10. In this study, the model with the lowest number of indicators and a prevalence of none of the classes of less than 5% was considered the optimal, practical model. After determining the optimal class and probabilistic allocation of the studied subjects to these classes, the relationship of these classes with the severity of Covid-19 adjusted for demographic variables was measured by multivariate logistic regression. The significance level was considered to be 0.05 in all analytical tests.

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Table 1 Frequency of some investigated variables according to the severity of Covid-19

Variables		Severity of disease Number (%)		P value
		Yes 4238(1.3)	No 314,264(98.7)	
Gender	Male	2431(1.4)	168,928(98.6)	< 0.001
	Female	1807(1.2)	145,336(98.8)	
Age	30–49	945(0.5)	200,033(99.5)	< 0.001
	50<=	3293(2.8)	114,231(97.2)	
Marital status	Single	2723(1.2)	217,182(98.8)	< 0.001
	Married	1515(1.5)	97,082(98.5)	
comorbidities	Yes	1623(2.1)	77,303(97.9)	< 0.001
	No	2615(1.1)	236,961(98.9)	
Vaccine status	Not vaccinated	2512(6)	39,257(94)	< 0.001
	1st dose	331(1.2)	27,216(98.8)	
	2nd dose	918(0.5)	175,840(99.5)	
	3rd dose	477(0.7)	71,951(99.3)	

Results

Of the 405,397 patients examined, 318,502 were 30 years or older. The average age and standard deviation were 47.5 years and 13.5, respectively. Of the patients, 171,359 (53.8%) were men and 147,143 (46.2%) were women. In terms of marital status, 219,905 patients (69%) were single and 98,597 (31%) were married. Of patients who had been vaccinated for Covid-19, 85.9% had received the first dose of vaccine, 78.7% the second dose of vaccine, and 23.3% the third dose of vaccine. In regard to the difference between the variables and the severity of Covid-19, men, patients over 50 years of age, married patients, and patients who had a comorbidity had more severe Covid-19 significantly ($p < 0.001$). Patients who had not received any doses of the Covid-19 vaccine had a higher rate of severe disease (6%) significantly compared with patients who had received one dose of vaccine (1.2%), two doses of vaccine (0.5%), or three doses of vaccine (0.7%) ($p < 0.001$) (Table 1).

The most common comorbidities in patients with Covid-19 were hypertension in 9.5%, metabolic disorders in 7.5%, hyperlipidemia in 7%, diabetes in 5.8%, and respiratory diseases in 4.8% (Table 2).

In terms of the relationship between underlying diseases and the severity of Covid-19, 3.4% of patients with diabetes, 3.3% with hypertension, 3.2% with cardiovascular diseases, 2.9% with ischemic heart disease, 2.3% with metabolic disorders, 2.2% with hyperlipidemia, and 2.2% with cancer had severe Covid-19 (Table 2).

After considering the fit of the model and the prevalence of each class in different classifications, class 3 was selected as the optimal class. The probability of the presence of different diseases in the three classes was checked, and, based on the contribution of each variable in different classes, the classes were named as follows:

Class 1 was patients with no multi-morbidity (83% patients) because the probability of these patients contracting different diseases was very low. Class 2 was patients who had hypertension, diabetes, respiratory diseases, and mental behavioral diseases (HRMD class, 9% patients). Class 3 was patients who had hypertension,

Table 2 Distribution of the frequency of different comorbiditoes according to the severity of the Covid-19

comorbidities	Disease in patients, N (%)	Severity of covid-19 N (%)		p-value
		Yes	No	
Hypertension	30,100(9.5)	997(3.3)	29,103(96.7)	< 0.001
Ischemic heart diseas	4823(1.5)	141(2.9)	4682(97.1)	< 0.001
Other cardiovascular disease	2462(0.8)	80(3.2)	2382(96.8)	< 0.001
Diabetes and other blood sugar disorders	18,402(5.8)	634(3.4)	17,768(96.6)	< 0.001
Hyperlipidemia	22,454(7)	491(2.2)	21,963(97.8)	< 0.001
Malnutrition	5056(1.6)	81(1.6)	4975(98.4)	0.091
Metabolic disorders	23,798(7.5)	541(2.3)	23,257(97.7)	< 0.001
cancer	3467(1.1)	77(2.2)	3390(97.8)	< 0.001
Parasitic infectious disease	9503(3)	172(1.8)	9331(98.2)	< 0.001
Diseases of the nervous system	2917(0.9)	59(2)	2858(98)	< 0.001
Thyroid disorder	4839(1.5)	63(1.3)	4776(98.7)	0.861
Musculoskeletal disorder	6167(1.9)	111(1.8)	6056(98.2)	0.001
Respiratory disease	15,410(4.8)	235(1.5)	15,175(98.5)	0.031
Gastrointestinal disease	7303(2.3)	121(1.7)	7182(98.3)	0.014
Genitourinary disease	7073(2.2)	116(1.6)	6957(98.4)	0.022
Behavioral mental disorders	16,366(5.1)	248(1.5)	16,118(98.5)	0.034
Eyes and ears diseases	3256(1)	61(1.9)	3195(98.1)	0.007
Blood and immune system diseases	4432(1.4)	75(1.7)	4357(98.3)	0.034
Total	78,926	4303	183,525	-

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Table 3 Probability of the presence of comorbidities in different classes of the optimal model

Classes of disease	Class 1	Class 2	Class 3
Hypertension	0.02	0.38	0.49
Hyperlipidemia	0	0	0.96
Ischemic heart disease	0.006	0.05	0.06
Cardiovascular disease	0.0008	0.04	0.03
Neurological diseases	0.001	0.05	0.03
Thyroid	0.005	0.06	0.06
Diabetes	0.01	0.23	0.35
Malnutrition	0.005	0.06	0.08
Metabolic disorders	0.0004	0.01	1
Cancer	0.0004	0.07	0.04
Infectious diseases	0.01	0.14	0.07
Immune system defect	0.001	0.09	0.04
Behavioral mental diseases	0.02	0.21	0.19
Eye and ear diseases	0.0009	0.06	0.04
Musculoskeletal diseases	0.001	0.12	0.08
Respiratory diseases	0.01	0.28	0.14
Digestive diseases	0.002	0.15	0.09
Venereal diseases	0.003	0.15	0.07
Estimated class population shares	0.83	0.09	0.07
Predicted class memberships	0.85	0.07	0.07

Table 4 Investigating some risk factors affecting the severity of covid-19 using multivariate logistic regression

Variables		OR	95% CI	*P*-value
Age	Under age 50 years	1	ref	< 0.001
	Over 50 years	6.99	6.48 ، 7.54	
Sex	female	1	ref	< 0.001
	male	1.39	1.30 ، 1.49	
Marital status	single	1	ref	0.123
	married	0.94	0.82، 1.01	
Vaccine status	Every vaccine dose	0.34	0.33,0.35	< 0.001
Disease class	No multi-morbidity	1	ref	-
	HRMD diseases	1.81	1.64 ، 1.99	< 0.001
	Metabolic diseases	1.55	1.40,1.72	< 0.001

OR: Odds Ratio, CI: Confidence Interval

hyperlipidemia, diabetes, and metabolic disorders. (metabolic disease class,7% patients) (Table 3).

Table 3 The multivariate logistic regression analysis showed that patients over 50 years of age had an increased odd of developing severe Covid-19 (i.e., almost seven times the risk of younger patients). Male patients had a 39% more odds of developing severe Covid-19 compared with women, patients suffering from HRMD diseases had 81%, and patients suffering from metabolic diseases had a 55% increased odds of severe Covid-19 compared to no multi-morbidity. Each additional dose of the COVID-19 vaccine was associated with a 66% lower risk of developing severe COVID-19 compared to patients who were not vaccinated. (Table 4).

Discussion

Comorbidities are major contributors to poor health and disability worldwide [14, 15]. The aging of the population and the coexistence of two or more diseases in elderly people [16, 17] have increased the importance of examining the pattern of multi-morbidities in COVID-19 patients. Our study aimed to investigate the prevalence and patterns of multi-morbidities in patients with COVID-19 and their relationship with disease severity. Our findings showed that the presence of multi-morbidities was significantly associated with COVID-19 severity, even after adjusting for age and sex. This is consistent with a systematic review and meta-analysis by Yang et al. [18], which found that comorbidities and age were important risk factors for severe COVID-19. Our study also demonstrated that men suffered from more severe COVID-19, aligning with studies by Fernandez-Nino [19] and Yang et al. [18].

The most common comorbidities in our COVID-19 patients were hypertension (9.5%), metabolic disorders (7.5%), hyperlipidemia (7%), diabetes (5.8%), and respiratory diseases (4.8%). These findings are somewhat similar to those reported by Yang et al. [18], who found hypertension in 17% of patients, diabetes in 8%, cardiovascular disease in 5%, and respiratory disease in 2%. Similarly, Bucholc et al. [20] reported hypertension in 22.7%, chronic obstructive pulmonary disease in 19.8%, and diabetes in 15.6% of COVID-19 patients.

People with comorbidities are at a higher risk of immune challenges for various reasons, including vulnerability to diseases and reduced resistance to health threats [21]. Specifically, cardiovascular diseases, diabetes, and metabolic problems increase the risk of mortality in COVID-19 patients due to vascular endothelial damage, hemostatic system dysfunction, and pro-inflammatory states or chronic inflammation [22, 23].

Our latent class analysis identified three distinct patterns of multi-morbidities: no multi-morbidity (83% of patients), HRMD diseases (hypertension, diabetes, respiratory diseases, and mental behavioral disorders; 9% of patients), and metabolic diseases (hypertension, hyperlipidemia, diabetes, and metabolic disorders; 7% of patients). Importantly, we found that the HRMD pattern increased the odds of severe COVID-19 by 81%, while the metabolic disease pattern increased the odds by 55%, compared to the no multi-morbidity group.

These findings are in line with previous studies, albeit with some differences in the magnitude of effect [24]. For instance, Guan et al. [3] reported higher odds of severe COVID-19 for patients with COPD (OR = 2.68), diabetes (OR = 1.58), hypertension (OR = 1.57), and cancer (OR = 3.50). Similarly, a meta-analysis by De Almeida-Pititto et al. [25] found odds ratios for severe disease and mortality of 2.35 and 2.50 for diabetes, 2.98 and 2.88 for

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hypertension, and 4.02 and 6.34 for cardiovascular disease, respectively.

The lower odds ratios observed in our study may be attributed to our classification method. Our reference group (no multi-morbidity) includes people with no diseases as well as those with other diseases at lower probabilities, potentially resulting in a higher baseline risk compared to studies where the reference group has no diseases at all.

Our findings regarding the impact of diabetes and hypertension on COVID-19 severity are particularly noteworthy, as these conditions are included in both the HRMD and metabolic disease patterns. This aligns with the study by Hernández-Gardu [26], which found that hypertension increased the probability of severe disease by 25% in women and 70% in men, while diabetes increased severity by 91% in women and 50% in men.

The mechanisms underlying the association between these comorbidities and COVID-19 severity are complex. For instance, the relationship between diabetes and severe COVID-19 may involve chronic inflammation, increased coagulation activity, immune response defects, and direct damage to the pancreas by SARS-CoV-2 [27]. Additionally, hypertension's impact may be related to the role of angiotensin-converting enzyme (ACE) as a binding site for SARS-CoV-2 [26].

Recent research has further emphasized the importance of considering multi-morbidity patterns in COVID-19 outcomes. A study by Carretero-Bravo J et al. [28] used latent class analysis, similar to our approach, to identify distinct multi-morbidity patterns among COVID-19 patients and found that certain combinations of comorbidities were associated with higher risks of adverse outcomes. Similarly, Ng et al. [29] employed machine learning techniques to identify clusters of comorbidities that were predictive of COVID-19 severity and mortality.

A meta-analysis by Ssentongo et al. [30] corroborated our findings on the impact of hypertension and diabetes, showing that these conditions, along with cardiovascular disease, were associated with increased risks of severe COVID-19 and mortality. Furthermore, Bello-Chavolla et al. [31] found that the combination of diabetes and obesity had a multiplicative effect on the risk of severe COVID-19, highlighting the importance of considering the interplay between different comorbidities.

Our study has some limitations, including the lack of data on some potentially influential factors such as BMI and the exact date of death for some patients. Future studies incorporating these variables could provide more detailed analyses. Also, the definition and measurement of multi-morbidity can vary across studies, which may affect the comparability of results [32]. Additionally, as pointed out by Zhang [33] the relationship between multi-morbidity can be due to their positive relationship with the body's immunity against disease.

However, a key strength of our study is its large sample size and comprehensive record of comorbidities. Unlike many previous studies that considered chronic diseases separately, our focus on multi-morbidities in COVID-19 patients provides a more nuanced understanding of at-risk groups, which can inform more effective treatment strategies and interventions.

Conclusion

The multi-morbidity patterns identified in our study offer a clear view of different risk groups among COVID-19 patients. The HRMD pattern, in particular, was associated with a substantially increased risk of severe COVID-19. These findings underscore the importance of considering multi-morbidity patterns, rather than individual comorbidities, in risk assessment and management of COVID-19 patients. Future research should focus on developing and validating risk prediction models based on these multi-morbidity patterns to guide clinical decision-making and resource allocation in the ongoing management of the COVID-19 pandemic.

Declarations

Ethics approval and consent to participate
In order to comply with ethical principles, informed written consent was received from the study participants and the purpose of the research and confidentiality of information was also explained to them during this process. This study was approved by the ethics committee of the Shahroud University of Medical Sciences, Shahroud, Iran (ethical cod: IR.SHMU.REC.1401.177).

Consent for publication
Participants provided their consent to publish this article.

Competing interests
The authors declare no competing interests.

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