

The impact of the cardiovascular risk factors on short-term in-hospital outcome of patients with COVID-19

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SOUHRN

Kontext: Infekční onemocnění covid-19 bylo spojeno s významnou morbiditou a mortalitou. Nepostihuje přitom pouze dýchací systém, ale byly pozorovány i četné systémové účinky jako myokarditida, arytmie a žilní tromboembolická nemoc.

Cíl studie: Naším cílem bylo zjistit frekvenci výskytu rizikových faktorů kardiovaskulárních onemocnění u pacientů s onemocněním covid-19 a dopady uvedených rizikových faktorů na krátkodobý výsledek nemocniční léčby pacientů s nově diagnostikovaným onemocněním covid-19.

Materiály a metody: Byla provedena průřezová analytická studie s 200 pacienty (průměrný věk $44,2 \pm 12,7$ roku) s onemocněním covid-19, prokázaným PCR testem, přijatými na izolační oddělení různých nemocnic v Egyptě. Pacientům byla odebrána anamnéza a byla provedena fyzikální vyšetření a vyšetření srdce. U zařazených pacientů se hodnotil profil kardiovaskulárního rizika. U všech pacientů byl natočen 12svodový elektrokardiogram, byly provedeny běžné laboratorní testy a vyšetření hrudníku výpočetní tomografií. Následně byli účastníci studie rozděleni do dvou skupin (A přeživší a B zemřelí). Údaje byly analyzovány statistickým softwarem pro sociální vědy verze 20.0 (SPSS Inc., Chicago, Illinois, USA).

Výsledky: Do studie bylo řazeno 200 pacientů ve věku 20 až 79 let, většinou mužů. Ve studii přežilo 181 účastníků (90,5 %; skupina A), 19 pacientů (9,5 %; skupina B) zemřelo. Multivariační analýza zjistila, že významnými prediktory úmrtní byly věk nad 60 let, systémová hypertenze, diabetes mellitus, obezita a dyslipidemie.

Závěry: U nepřeživších účastníků studie s onemocněním covid-19 byly častěji přítomny systémová hypertenze, diabetes mellitus, obezita a dyslipidemie.

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ABSTRACT

Background: Coronavirus disease (COVID-19) has caused significant morbidity and mortality. COVID-19 is more than a respiratory illness, it had multiple systemic effects such as myocarditis, arrhythmias, and venous thromboembolism.

Aim of the study: We aimed to study the frequency of cardiovascular risk factors in patients with COVID-19 and the impact of these risk factors on short-term in-hospital outcome of patients newly discovered with COVID-19.

Materials and methods: Cross-sectional analytic study conducted in Egypt on 200 patients (mean age of 44.2 ± 12.7 years old) with positive polymerase chain reaction for COVID-19 recruited from different isolation hospitals. Patients were subjected to history taking, physical examination, and cardiac examination. The cardiovascular risk profile was studied among the enrolled patients. Twelve-lead electrocardiogram, routine laboratory tests, and computed tomography chest study were done for all patients. Patients were grouped into two groups A and B for survivors and non-survivors, respectively. Data were entered using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA).

Results: The study was conducted on two hundred patients aged 20 to 79 years with male predominance. The study found that 181 patients (90.5%) survived (Group A) and 19 patients (9.5%) died (Group B). Multivariate analysis revealed that significant predictors of death were age above 60 years old, systemic hypertension, diabetes mellitus, obesity and dyslipidemia.

Conclusions: Systemic hypertension, diabetes mellitus, obesity, and dyslipidemia were more prevalent in non-survivor patients with COVID-19.

Keywords:

COVID-19

Diabetes mellitus

Systemic hypertension

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Introduction

Coronaviruses which belong to the Corona viridae family are characterized by having crown-like spikes on the outer surface of the virus. These small sized viruses (65–125 nm in diameter) contain a single-stranded RNA as a nucleic material whose length ranges from 26 to 32 kbs in length (Fig. 1).¹

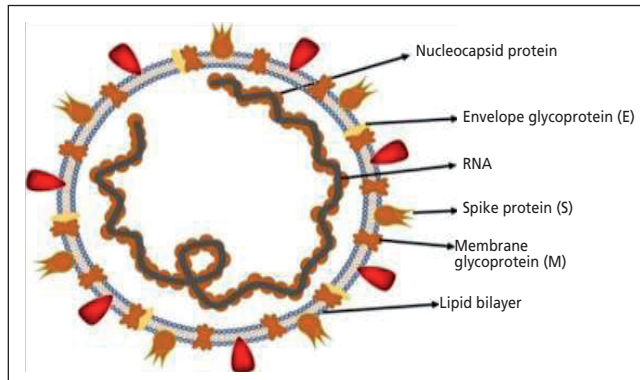


Fig. 1 – Structure of the human coronavirus causing respiratory syndrome.¹

At the end of 2019 an outbreak of coronavirus that killed more than eighteen hundred and infected over seventy thousand individuals within the first fifty days of the epidemic happened in Wuhan, China. This virus was found to be a member of the coronaviruses β group. The Chinese researchers named it as 2019 novel coronavirus (2019-nCoV). The International Committee on Taxonomy of Viruses called the virus as SARS-CoV-2 and the disease as COVID-19.²⁻⁴

Coronaviruses family subgroups are alpha (α), beta (β), gamma (γ), and delta (δ) coronavirus. Severe acute respiratory syndrome coronavirus (SARS-CoV), H5N1 influenza A, H1N1 2009 and Middle East respiratory syndrome coronavirus (MERS-CoV) cause acute lung injury and respiratory distress syndrome which leads to respiratory failure.¹

Seventeen mutations in the viral genome are found in the alpha variant. Eight mutations (Δ 69–70 deletion, Δ 144 deletion, N501Y, A570D, P681H, T716I, S982A, and D1118H) are in the spike (S) protein. N501Y shows an increased affinity of the spike protein to angiotensin-converting enzyme 2 receptors, which facilitates the viral attachment and the subsequent entry into host cells.⁵

Compared to other SARS-CoV-2 variants, alpha variant was associated with increased mortality.⁶ A second wave of COVID-19 infections was first detected in South Africa in October 2020. This wave was caused by Beta variant with multiple spike mutations.⁷

In December 2020, Gamma variant was found in Brazil and was first detected in United States in January 2021.⁸ Delta variant was initially identified in December 2020 in India and was responsible for the second wave of COVID-19 infections in April 2021 in India. On the 23rd November 2021, Omicron variant was found in South Africa after a small increase in the number of cases of COVID-19.⁹ Omicron caused a 13-fold increase in viral infectivity and

was found to be 2.8 times more infectious than the Delta variant.¹⁰ The virus had incubation period ranged from 0 to 24 days, with an average of 5–7 days.¹¹

Individuals of any age were susceptible to the infection. Most of the patients presented with mild to moderate symptoms. It was found that the most common symptoms were fever, fatigue, dry cough, and upper respiratory tract symptoms. However, one report described patients with gastrointestinal symptoms in children and adolescents.¹²

It was found that the overall case-fatality rate of COVID-19 was 2.3% with approximately 20% of patients having developed severe respiratory illness. Moreover, fever, dry cough, dyspnea, and bilateral pulmonary infiltrates on chest imaging were found in patients with severe disease. Complications of COVID-19 included respiratory failure, acute myocardial injury, acute kidney injury, liver injury, septic shock, and multiple organ failure. Moreover, severe symptoms were likely to occur in the elderly males and in those with underlying co-morbidities.¹³ Lymphopenia was frequently found in COVID-19 patients.¹⁴

Chest computed tomography (CT) early findings in patients with COVID-19 included single or multiple limited patchy shadows with interstitial changes, located at the peripheral lung fields just inside the pleura. Moreover, positive bronchus signs and thickening of the blood vessels could be detected. Ultimately, lesions might progress to multiple ground glass opacities bilaterally (Fig. 2).¹⁵

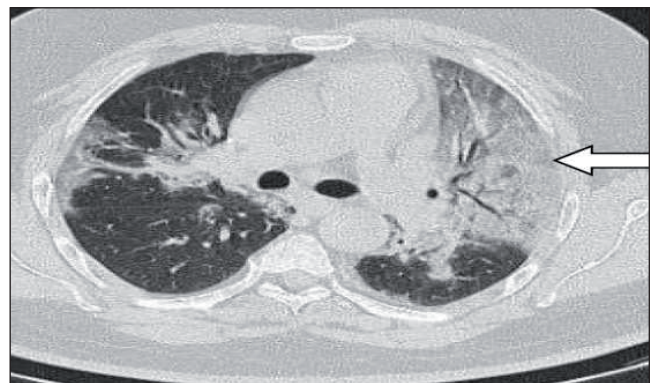


Fig. 2 – Ground glass infiltration with air bronchogram of a patient with COVID-19.¹⁵

Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) is a diagnostic test that uses nasal swab, tracheal aspirate or bronchoalveolar lavage specimens. The preferred method for diagnosis is the collection of upper respiratory samples using nasopharyngeal and oropharyngeal swabs.¹⁶

Although there might be false positive results due to swab contamination especially in asymptomatic patients, it was found that the specificity of the RT-PCR test was very high. The sensitivity rate was not clear, but was found to be around 66–80%.¹⁷ Moreover, it was found that single negative test did not rule out SARS-CoV-2 infection, especially if the nasopharyngeal swab specimen was taken from highly exposed persons at the beginning of the infection.¹⁷

Cardiovascular risk factors and COVID-19

SARS-CoV-2 was reported to directly infect the endothelium and possibly the heart which could precipitate cardiovascular complications. Isolated cases of fulminant myocarditis or pericarditis were attributed to COVID-19.¹⁸

It was found that in diabetic patients, the natural immunity is compromised due to elevated blood glucose levels, so glycosylation of cytokines will affect the function of cytokines dependent on type I helper T lymphocytes. Pulmonary microangiopathy and tissue damage caused by oxidative stress in hyperglycemia predispose the patients to COVID-19.¹⁹

By binding angiotensin-converting enzyme 2 receptors, SARS-CoV-2 could destroy pancreas islet cells. High blood glucose in patients may decrease immune response to SARS-CoV-2 and inhibit neutrophil chemotaxis, phagocytosis, and intracellular killing, resulting in more drastic and prolonged disease.²⁰

SARS-CoV-2 enters cells through angiotensin-converting enzyme 2 (ACE2) receptors therefore medication with angiotensin-receptor blockers (ARBs) may be associated with increased ACE2 expression and susceptibility to COVID-19.²¹

High prevalence of systemic hypertension among hospitalized COVID-19 patients as well as patients with severe illness were reported.²²

Despite these observations, the association between hypertension and COVID-19 was still unclear. Although, overrepresentation of systemic hypertension was seen in patients admitted to hospitals with COVID-19, it was unclear whether this association was due to the older age of these patients, presence of other comorbidities or just a simple random association.²³

It was found that considerable energy was used by the obese patients to overcome the reduction in chest wall compliance. Moreover, considerable energy must be spent to overcome the air flow limitation and the airway resistance. Taken all together, the respiratory system of obese subjects can be severely affected by any respiratory insults like COVID-19.²⁴

It was found that abnormal blood lipids (dyslipidemia) could affect the outcome of COVID-19 patients. Since cholesterol is the major neutral lipid of pulmonary surfactant so hypercholesterolemia can disrupt the protective features of surfactant in alveolar spaces. Moreover, since cholesterol is a major structural component of immune cell membranes, elevated cholesterol levels can affect pulmonary immune responses and exacerbate pulmonary inflammation response.²⁵

The current study aims to study not only the frequency of cardiovascular risk factors in patients with COVID-19 but also the impact of cardiovascular risk factors on the short-term in-hospital outcome of patients newly discovered with COVID-19.

Patients and methods

This cross-sectional analytic study was carried out at different isolation hospitals, Cairo, Egypt during the period extending from January 2021 to September 2021. The

study protocol was approved by the local ethical committee and was given an approval number (142-2021). This study was carried out on 200 patients above 18 years old admitted with positive polymerase chain reaction for COVID-19 with at least one of the cardiovascular risk factors.

Patients were subjected to history taking, physical examination, and cardiac examination. The cardiovascular risk profile was studied among the enrolled patients. Systemic hypertension was diagnosed if the systolic blood pressure was ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg or if the patient was on antihypertensive medication.²⁶

Diabetes mellitus was diagnosed by measuring HbA_{1c} if equal or more than 6.5%, fasting blood glucose level equal or more than 126 mg/dl, post prandial blood glucose level equal or more than 200 mg/dl or if the patient was on antidiabetic medications.²⁷

Dyslipidemia was diagnosed by measuring low-density lipoprotein if equal or more than 100 mg/dl, high-density lipoprotein equal or lower than 40 mg/dl in females or 50 mg/dl in males, triglycerides level equal or more 200 mg/dl or if the patient was on lipid lowering medications.²⁸

Obesity was diagnosed by measuring body mass index if more than 30 kg/m² which was obtained by dividing the patient weight by the square of his height.²⁹

The short in-hospital course of the enrolled patients was followed clinically, using standard twelve-lead electrocardiogram, laboratory investigations and by computed tomography chest study. Patients were grouped to survivors and non-survivors.

The short-term in-hospital course of the patients was followed regarding the decline in oxygen saturation, the need for continuous positive airway pressure, and invasive versus non-invasive mechanical ventilation.

Administration of ventilatory support without using an invasive artificial airway (endotracheal tube or tracheostomy tube) was defined as noninvasive ventilation.³⁰

The invasive mechanical ventilation defined as the use of endotracheal tubes and mechanical ventilators³¹ not only protects the airway but also helps suctioning of respiratory secretions and stabilizes patients with hypoxemic and hypercapnic respiratory failure.³²

Continuous positive airway pressure (CPAP) therapy utilizes machines designed to deliver a flow of constant pressure. CPAP can be administered as nasal, nasopharyngeal using the nasopharyngeal tube or via face mask.³³

Statistical analysis

Data were coded and entered using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean \pm standard deviation (SD).

Qualitative data were expressed as frequency and percentage. Comparison between groups with qualitative data was done using **Chi-square test** and **Fisher's exact test** instead of Chi-square test only when the expected count in any cell less than 5.

Multivariate logistic regression analysis: Odds ratios (OR) with 95% confidence intervals were computed to assess the overall association between each possible risk factor and the outcome. The confidence interval was set

to 95% and the margin of error accepted was set to 5%. $P\text{-value} \leq 0.05$ was considered statistically significant.

Results

This cross-sectional analytic study was carried out in different isolation hospitals in Cairo, Egypt during the period extending from January 2021 to September 2021.

The study was done on 200 patients with positive polymerase chain reaction for COVID-19 with at least one of the well-known cardiovascular risk factors, e.g. systemic hypertension, diabetes mellitus, dyslipidemia, obesity or smoking. A written consent was taken from all the enrolled patients to participate in the study. The enrolled patients aged from 20 to 79 years old (mean age of 44.3 ± 12.7 years). The study included 181 patients (90.5%) younger than 60 years and 19 patients (9.5%) older than 60 years. Moreover, 104 patients (52%) were males and 96 patients (48%) were females. The demographic data of the enrolled patients are demonstrated in Table 1.

One hundred and twenty one patients (60.5%) were hypertensive, 98 patients (49.0%) were diabetics, 106 patients (53.0%) were smokers, 54 patients (27.0%) were obese and 42 patients (21.0%) had dyslipidemias. Table 2 illustrates the cardiovascular risk profile of the enrolled patients.

The short-term in-hospital course of the patients was followed. Patients were grouped to survivors and non-survivors (group A and B, respectively). The study found

Table 1 – Demographic data distribution among patients with COVID-19

Demographic data	Number of patients (n = 200)	Percentage
Age (years)		
<60 years	181	90.5%
≥60 years	19	9.5%
Gender		
Female	96	48.0%
Male	104	52.0%

that among COVID-19 patients 121 (60.5%) had oxygen saturation $>90\%$ and 79 patients (39.5%) had oxygen saturation $<90\%$ (Fig. 3).

Invasive mechanical ventilation (MV) was required in 54 patients (27%) with COVID-19. Fifty-six patients (28%) were treated with continuous positive airway pressure (CPAP) and 180 patients used nasal cannulas and oxygen masks. Most of the patients who did not survive were above 60 years old (89.5%) which indicated bad outcome of elderly COVID-19 patients older than 60 years (Table 3).

Systemic hypertension was more prevalent in non-survivor group (100%) compared to survivor group (56.4%). Diabetes mellitus was prevalent in non-survivor group (100%) compared to survivor group (43.6%) (Fig. 4).

Table 4 illustrates the short-term in-hospital outcome of the study groups regarding the oxygen saturation, the need for invasive mechanical ventilation, continuous positive airway pressure or oxygen therapy.

Table 2 – Cardiovascular risk profile of the enrolled patients

Cardiovascular risk factors	Number of patients	Percentage
HTN		
No	79	39.5%
Yes	121	60.5%
DM		
No	102	51.0%
Yes	98	49.0%
Smoking		
No	94	47.0%
Yes	106	53.0%
Obesity		
No	146	73.0%
Yes	54	27.0%
Dyslipidemia		
No	158	79.0%
Yes	42	21.0%

DM – diabetes mellitus; HTN – systemic hypertension.

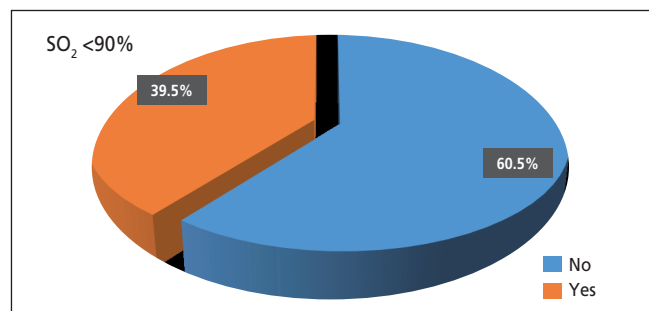


Fig. 3 – Oxygen saturation (SO₂) <90% distribution among patients with COVID-19.

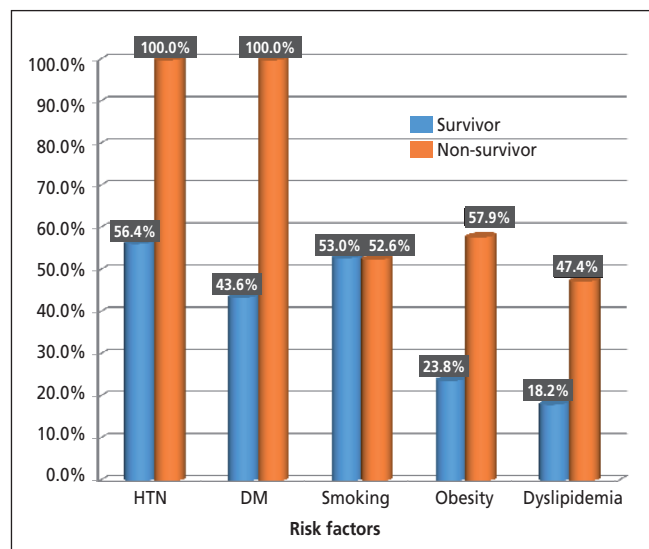


Fig. 4 – The cardiovascular risk factors among the study groups. DM – diabetes mellitus; HTN – hypertension.

Table 3 – The demographic data of the study groups

Demographic data	In-hospital outcome				Total		P-value
	Survivor (n = 181)		Non-survivor (n = 19)				
	N	%	N	%	N	%	
Age (years)							
<60 years	179	98.9%	2	10.5%	181	90.5%	<0.001**
≥60 years	2	1.1%	17	89.5%	19	9.5%	
Gender							
Female	87	48.1%	9	47.4%	96	48.0%	0.954
Male	94	51.9%	10	52.6%	104	52.0%	

P-value >0.05 non-significant.

** P-value <0.001 highly significant.

Table 4 – Oxygen saturation, the need for invasive MV, CPAP, and oxygen therapy among the study groups

	Outcome				Total		P-value
	Survivor (n = 181)		Non-survivor (n = 19)				
	N	%	N	%	N	%	
SO ₂ <90%							
No	121	66.9%	0	0.0%	121	60.5%	<0.001**
Yes	60	33.1%	19	100.0%	79	39.5%	
Invasive MV							
Non-invasive MV	146	80.7%	0	0.0%	146	73.0%	<0.001**
Invasive MV	35	19.3%	19	100.0%	54	27.0%	
CPAP							
No	125	69.1%	19	100.0%	144	72.0%	0.004*
Yes	56	30.9%	0	0.0%	56	28.0%	
O ₂ mask & nasal							
No	1	0.6%	19	100.0%	20	10.0%	<0.001**
Yes	180	99.4%	0	0.0%	180	90.0%	

* P-value <0.05 significant; ** p-value <0.001 highly significant. CPAP – continuous positive airway pressure; MV – mechanical ventilation; O₂ – oxygen; SO₂ – oxygen saturation.

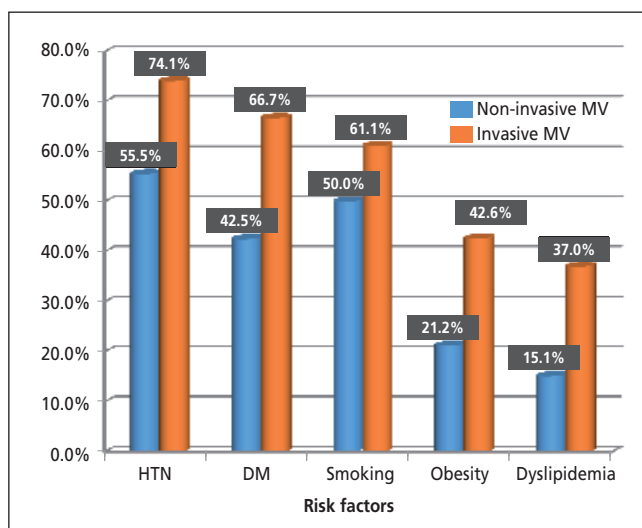


Fig. 5 – The cardiovascular risk profile of the invasive and noninvasive mechanically ventilated patients. DM – diabetes mellitus; HTN – systemic hypertension; MV – mechanical ventilation.

Systemic hypertension was found in 74.1% of the invasive MV group patients versus 55.5% of the non-invasive MV group. Diabetes mellitus was more prevalent in the invasive mechanically ventilated group versus the non-invasive group (66.7% versus 42.5%).

Figure 5 presents the cardiovascular risk profile of the mechanically ventilated patients. Moreover, multivariate analysis revealed that significant predictors of mortality were age above 60 years, systemic hypertension, diabetes mellitus and obesity (p-value <0.001, 0.003, 0.002, and 0.038, respectively).

Discussion

This was a cross-sectional analytic study conducted on 200 COVID-19 patients aimed to study the cardiovascular risk factors and outcomes in COVID-19 hospitalized patients.

The enrolled patients were admitted with positive polymerase chain reaction for COVID-19 from different

isolation hospitals in Egypt with at least one of the risk factors as hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking.

The study was conducted on a wide age group ranging from 20 to 79 years, (mean age of 44.3 ± 12.7 years). There were 181 patients (90.5%) below 60 years old and 19 patients (9.5%) above 60 years old. Concordant with other studies,^{34,35} most of the patients were males (56.8%).

A recent prospective cohort study identified risk factors for in-hospital mortality and major adverse cardiovascular events among hospitalized adults with COVID-19 and found that 60.2% were hypertensive, 39.8% were diabetics and 38.6% had hyperlipidemia.³⁶

We found that 121 patients (60.5%) were hypertensive; 98 patients (49.0%) were diabetics; 106 patients (53.0%) were smokers; 54 patients (27.0%) were obese and 42 patients (21.0%) had dyslipidemias.

It was found that among approximately 9000 patients hospitalized for COVID-19 in North America, Europe, and Asia, 30.5% had hyperlipidemia, 26.3% had arterial hypertension, 14.3% had diabetes mellitus, 16.8% were former smokers, and 5.5% were current smokers.³⁷ In agreement with other studies,³⁸ we found that among the enrolled COVID-19 patients, 181 patients (90.5%) survived.

Collard et al.³⁸ observed a stronger association between hypertension, diabetes, dyslipidemia, and mortality in COVID-19 patients compared with previous studies on community-acquired pneumonia, despite a similar prevalence of cardiovascular risk factors risk factor.

Nicholson et al.³⁴ reported that, among the 1042 patients admitted to hospital, 832 (79.8%) were discharged and 210 (20.2%) died in hospital. The patients in our study were grouped to survivors and non-survivors. Elderly patients older than 60 years were more prevalent in non-survivor group (89.5%) compared to survivor group (1.1%).

In agreement with Collard et al.,³⁸ we found that systemic hypertension, diabetes mellitus, obesity and dyslipidemia were more prevalent in non-survivors compared to survivors (100% versus 56.4% p -value < 0.001 , 100% versus 43.6% p -value < 0.001 , 57.9% versus 23.8% p -value < 0.001 , and 47.4% versus 18.2% p -value = 0.003, respectively).

Oxygen dropped below $< 90\%$ in all the non-survivors versus 33.1% of the survivors. Invasive MV was needed in all the non-survivors versus (19.3%) of survivors.

The objectives of the mechanical ventilation are the maintenance of exchange gas, correction of hypoxemia and respiratory acidosis, avoid fatigue of the respiratory muscles and reduce oxygen consumption.

Patel et al.³⁹ aimed to identify risk factors associated with poor outcomes (invasive mechanical ventilation and mortality) of COVID-19 hospitalized patients. They found that COVID-19 patients with coexisting comorbidities such as cardiovascular disease, cerebrovascular disease, and chronic liver disease had poor outcomes like death and the need for invasive mechanical ventilation compared with those without comorbidities. They recommended good medical history taking as this will help in identification of high-risk patients who are prone to develop adverse outcomes of COVID-19.

Noninvasive ventilation defined as a ventilation modality that supports breathing by delivering mechanically assisted

breaths without the need for intubation or surgical airway was found in 146 patients (73%) of the current study.

Invasive MV defined as the delivery of positive pressure to the lungs via an endotracheal or tracheostomy tube was needed in 27% of our population. Moreover, oxygen saturation dropped below 90% in all non-survivor patients versus 33.1% of the survivors.

The current study found that elderly patients older than 60 years were more prevalent in invasively mechanically ventilated patients versus non-invasive mechanically ventilated (33.3% versus 0.7%).

A multicenter prospective observational study that enrolled 391 patients from fifteen COVID-19 dedicated Italian intensive care units underwent invasive mechanical ventilation for COVID-19 pneumonia and found that age, the Sequential Organ Failure Assessment (SOFA) score at ICU admission, respiratory system compliance, renal and cardiovascular complications and late-onset ventilator-associated pneumonia were independent risk factors for prolonged mechanical ventilation in patients with COVID-19.⁴⁰

Increasing age was significantly associated with a higher duration of MV and intensive care unit mortality and this is in line with recent literature on COVID-19 patients.⁴¹

The current study found that systemic hypertension, diabetes mellitus, obesity, and dyslipidemia were more prevalent in invasive MV compared to noninvasive MV (74.1% versus 55.5% p -value = 0.017, 66.7% versus 42.5% p -value = 0.002, 42.6% versus 21.2% p -value = 0.003 and 37% versus 15.1% p -value < 0.001 , respectively).

Nicholson et al., 2021³⁴ reported certain variables that were associated with the need for mechanical ventilation in patients with COVID-19. These variables included diabetes mellitus (p -value = 0.001), $\text{SpO}_2 : \text{FiO}_2$ ratio, C-reactive protein and lactate dehydrogenase.

On the other hand, Jewbali et al., 2021⁴² reported that they could not conclude which cardiovascular risk factors, cardiovascular diseases or cardiovascular history can predict hospital admission or mortality in COVID-19 patients due to a lack of studies on multivariable models taking age into account.

Concordant with our findings, it was found that obesity is a risk factor of poor outcome of COVID-19. Body mass index is an important routine procedure that should be assessed in COVID-19 patients and special attention should be given to patients with obesity.⁴³

In agreement with other studies,⁴⁰ continuous positive air way pressure was used frequently in invasive MV versus non-invasive MV (64.8% versus 14.4% $p < 0.001$). On the other hand, oxygen therapy by mask was used frequently in non-invasive MV group (99.3%) compared to invasive MV group (64.8%) (p -value < 0.001).

Conclusion

The accumulation of traditional cardiovascular risk factors leads to a stepwise increased risk for short-term mortality in hospitalized COVID-19 patients. Hospitalized COVID-19 patients with underlying cardiovascular risk factors appear to be at risk of poor outcome. Further studies investigating how these risk factors disproportionately affect COVID-19 patients are needed.

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Conflict of interest

None declared.

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