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The Impact of Co-morbidities on Hospitalized Syrian Patients with Covid-19

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Abstract:

Objectives

This study aims to compare the clinical manifestations, laboratory findings, outcomes, and the overall survival time of Covid-19 patients with different co-morbidities.

Design

Retrospective design.

Setting

This multicenter study was undertaken at two hospitals in Damascus, Syria.

Participants

A total of 515 Syrian patients met the inclusion criteria, laboratory- confirmed Covid-19 infection in accordance with Centers for Disease Control and Prevention. Exclusion criteria were suspected and probable cases that were not confirmed with a positive reverse transcription-polymerase chain reaction assay; and patients who self-discharged from the hospital against medical advice.

Primary and secondary outcome measures

The first, assess the impacts of co-morbidities with Covid-19 infection in 4 areas (clinical manifestations, laboratory findings, and outcomes). The second, Covid-19 patients with co-morbidities overall survival time.

Results

Of 515 patients included, 316 (61.4%) were male, and 347 (67.4%) had at least one coexisting chronic disease. Patients with co-morbidities compared with no co-morbidities were more vulnerable to poor outcomes such as severe infection (32.0% vs. 9.5%, p-value < .001), severe complications (34.6% vs. 9.5%, p-value < .001), the need for mechanical ventilation (28.8% vs. 7.7%, p-value < .001), and death (32.0% vs. 8.3%, p-value < .001). Multiple logistic regression showed that patients ≥ 65 years old, positive smoking history, patients with ≥ 2 co-morbidities, and patients with chronic obstructive pulmonary disease were risk factors linked to severe Covid-19 infection in patients with co-morbidities. Overall survival time was lower among patients with co-morbidities (vs. no co-morbidities), patients with ≥ 2 co-morbidities (vs. one co-morbidity), patients with hypertension, chronic obstructive pulmonary disease, malignancy, or obesity (vs. other co-morbidities) (p-value < 0.05).

Conclusion

Patients with co-morbidities should weigh the odds of the rare side effects identified with the Covid-19 vaccine against the known higher risks of contracting Covid-19 infection.

Strengths and limitations of this study:

. Data collection issues include disorganized files, subjective records, lost records, and illegible handwriting.

. Information gathered covered co-morbidities, clinical manifestations, laboratory findings, and outcomes of hospitalized Covid-19 patients.

. Results deduced acquire methods to mitigate the spread of Covid-19 among those vulnerable with co-morbidities.

. The retrospective design of the study is inferior in evidence compared with prospective studies.

Keywords: Syrian Arab Republic, SARS-CoV-2, War.

Introduction:

Since Coronavirus Disease 2019 (Covid-19) was first recognized in December 2019,[1] a collaborative effort focused on understanding the epidemiological, demographic, and clinical features of this virus was triggered. Covid-19 continues to spread, infecting over half a billion and killing millions.[2] Despite the thousands of published medical research and the milestones, we have overcome, the virus continues to cause unpredictable chaos.[3] One observation quickly noticed by the medical community after the start of the epidemic was that Covid-19 affects people differently, with most cases showing mild symptoms; however, many studies revealed that the presence of co-morbidities can be associated with more severe infection cases and clinical complications.[4] [5] [6] Approximately one in five individuals are at increased risk of severe Covid-19.[7] After these results were announced around the world, it is not surprising that generalized anxiety and Covid-19-related fear were elevated among individuals with high-risk diseases such as diabetes, hypertension, cardiovascular, and chronic respiratory diseases.[8] In light of this crisis, the medical community has agreed that vaccines remain the only way to fight the pandemic, and in December 2020 the United States Food and Drug Administration (FDA) issued an emergency use authorization to facilitate the use and availability of Covid-19 vaccines.[9] Despite the conformation about the efficacy and safety of Covid-19 vaccines,[10, 11] vaccine hesitancy worldwide became a big

obstacle in the vaccination process.[12] In Syria, only 9.3% of the population is fully vaccinated,[13] with vaccine hesitancy higher among people with a history of chronic co-morbidities.[14] Many studies showed that people with co-morbidities had greater odds of developing severe post-vaccination side effects.[15] [16] To accurately study the impact of co-morbidities on the severity of Covid-19 infection and thus confirm the importance of protecting this vulnerable group, this study was conducted to evaluate the impact of co-morbidities on the clinical manifestations, laboratory findings, and outcomes of Covid-19 infected patients. The objective was to study the differences in outcomes and overall survival time (OS) between Covid-19 patients with different types of co-morbidities.

Methods:

Study Design, settings, and participants

This retrospective, multicenter, observational study was conducted at two main Hospitals in Damascus and Rural-Damascus, Damascus Hospital (Al-Mujtahid) and Al- Mouwasat Hospital, between 1/9/2021 and 30/9/2021. Al-Mouwasat Hospital is affiliated with the Syrian Ministry of higher education and scientific research. Damascus Hospital is affiliated with the Syrian Ministry of health. Damascus Hospital and Al-Mouwasat Hospital were emergency hospitals involved in the isolation and management of patients with Covid-19 during the outbreaks. A total of 515 patients with confirmed COVID-19 diagnoses were enrolled in this study.

Inclusion criteria

Inclusion criteria were laboratory- confirmed Covid-19 infection following the Centers for Disease Control and Prevention (CDC) published criteria.[17] [18]

Exclusion criteria

Exclusion criteria were suspected and probable cases that were not confirmed with a positive reverse transcription-polymerase chain reaction (RT-PCR) assay; and patients who self-discharged from the hospital against medical advice, and therefore, missed their outpatient follow-up.

Data collection

Clinical records and laboratory results were reviewed by the authors. Furthermore, the authors contacted patients via

telephone when data from files were incomplete. The data collected included socio-demographic features: age, sex, and smoking history; vital signs: temperature, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure; clinical symptoms: dry cough, dyspnea, fever, chills, weakness and fatigue, oedema, sore throat, chest pain, headache, runny nose, anosmia, ageusia, arthralgia, myalgia, irritability, confusion, loss of consciousness, nausea, vomiting, diarrhea, abdominal pain, lethargy, bradyglossia, anorexia, and weight loss; co-morbidities: hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month; complications: acute respiratory distress syndrome (ARDS), heart failure, acute renal injury, cute liver injury, and septic shock; laboratory results on admission: complete blood count, kidney function tests, liver function tests, D-dimer, and C-reactive protein (CRP); radiological assessment; RT-PCR results; clinical outcomes: complete recovery, need for oxygen therapy, need for mechanical ventilation, and death.

Two investigators separately checked the data collection to confirm the accuracy of the data gathered. Patients were classified into two groups, the first group, Covid-19 patients with at least one of the following co-morbidities, hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month; the second group, Covid-19 patients without any co-morbidity.

Ethical Approval

This study was approved by the ethics committee of Damascus Hospital, Syrian Ministry of Health. This study was not granted a specific identification number.

Study Definitions

Manifestations found on chest x-ray and computed tomography (CT) scans were reviewed by an attending physician in the Respiratory department. ARDS was diagnosed when someone with a confirmed Covid-19 infection met the Berlin 2012 ARDS diagnostic criteria: 1) acute hypoxemic respiratory failure 2) presentation within 1 week of worsening respiratory symptoms 3) bilateral airspace disease on chest x-ray, CT, or ultrasound that is not fully explained by effusions, labor or lung collapse, or nodules 4) cardiac failure is not the primary cause of acute hypoxemic respiratory

failure.[19] Covid-19 infection severity was divided into three groups: mild, moderate, and severe based on the National Institutes of Health Covid-19 treatment guidelines.[20]

Patient and public involvement

The public was not involved in the study design, conduct of the study, or plans to disseminate the results to study participants.

Statistical Analysis

Categorical variables were reported as frequencies and percentages (descriptive Statistics), and continuous variables were presented as the mean with standard deviation. The t-test was conducted to compare the laboratory results between Covid-19 patients with co-morbidities and Covid-19 patients without co-morbidities. The chi-square was used to compare 2 groups, Covid-19 patients with co-morbidities and Covid-19 patients without co-morbidities, against socio-demographic features, clinical manifestations, complications, and outcomes. The chi-square test was also used to compare Covid-19 patients with different co-morbidities (hypertension, diabetes mellitus, cardiovascular disease, COPD, malignancy, and obesity) against severe infection, complications (ARDS, heart failure, acute renal injury, acute kidney injury, and septic shock), mechanical ventilation, and death. Multivariable logistic regression was performed to detect factors associated with severe Covid-19 infection (vs. no severe Covid-19 infection), selected factors included age (≥ 65 years vs. < 65 years), sex (male vs. female), smoking history (positive smoking history vs. negative smoking history), number of co-morbidities (≥ 2 co-morbidities vs. one co-morbidity), and type of co-morbidities (hypertension vs. diabetes mellitus, cardiovascular diseases, COPD, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month), (diabetes vs. hypertension, cardiovascular diseases, COPD, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month), and (COPD vs. hypertension, diabetes mellitus, cardiovascular diseases, chronic, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month). For survival analysis, the set time from the presence of symptoms until death or the last follow-up (30 September 2021) was used. The Kaplan-Meier survival curves were conducted and differences in survival rate were analyzed by log-

rank test. All statistical analyses were performed using the statistical package for social sciences (SPSS) statistics version 25.0. A statistically significant p-value was set at < 0.05.

Results:

Socio-demographic features clinical manifestations, complications, and outcomes of Covid-19 Patients

A total of 515 patients with Covid-19 were included in this study. The median age was 60 years, and the range was between 16 and 95 years. Males represented 316 (61.4%) and females represented 199 (38.6%). 192 (37.3%) patients were current or previous smokers. Of 347 (67.4%) patients with co-morbidities, 196 (56.6%) have hypertension, 149 (42.9%) have diabetes mellitus, 102 (29.4%) have cardiovascular diseases,43 (12.4%) have renal disease, 42 (12.1%) are obese, 35 (10.1%) have COPD, 34 (9.8%) have malignancies, 29 (8.4%) have neurological disease, 23 (6.6%) have autoimmune disease, 14 (4.0%) have hematological disease, 13 (3.7%) have gastrointestinal and liver diseases, and 13 (3.7%) had surgery within the last month. 189 (36.7%) reported having two or more co-morbidities. Patients with co-morbidities were older (mean = 63.9 years) compared with patients with no co-morbidities (mean = 52.7 years). Also, patients with co-morbidities had a higher positive smoking history (40.6%) compared with no co-morbidities (30.4%). Patients with co-morbidities had higher mean temperatures (38.0 ± 0.9°C), heart rates (94.5 ± 17.6 beats per minute), systolic blood pressures (124.3 ± 21.2 mmHg), and diastolic blood pressures (76.1 ± 13.6 mmHg) on admission compared with patients without co-morbidities (p-value = 0.009), (p-value < .001), (p-value < .001), and (p-value < .001) respectively. The most common symptoms among Covid-19 patients were dry cough 380 (73.8%), weakness and fatigue 374 (72.6%), fever 357 (69.3%), and dyspnea 357 (69.3%). The predominant clinical presentation among Covid-19 patients with co-morbidities was dyspnea 267 (76.9%), followed by dry cough 250 (72.0%), fever 242 (69.7%), and weakness and fatigue 242 (69.7%). Whereas, weakness and fatigue 132 (78.6%) was the most common clinical symptom among Covid-19 patients without co-morbidities. Patients with co-morbidities were more likely to suffer from dyspnea (76.9%) compared with patients without co-morbidities (53.6%) (p-value < .001) (Table 1).

Regarding Covid-19 severity, most patients had moderate disease 203 (39.4%). Patients without co-morbidities were more likely to experience mild disease 98 (58.3%). 127 (24.6%) patients developed severe Covid-19, severe infection was

more common among patients with at least one co-morbidity 111 (32.0%) compared with those without co-morbidities 16 (9.5%) (p-value < .001). A comparison of Covid-19 infection severity between patients with different co-morbidities showed that patients who had surgery during the last month were more likely to develop severe infection 9 (69.2%), followed by patients with malignancies 22 (64.7%), and COPD 20 (57.1%). A total of 457 (88.7%) patients required oxygen support. Patients with co-morbidities were more vulnerable to poor outcomes including severe complications compared with patients without co-morbidities 34.6% and 9.5% respectively (p-value < .001). Patients with co-morbidities were associated with the need for mechanical ventilation (28.8%) compared with patients without co-morbidities (7.7%) (p-value < .001). Patients with co-morbidities were more likely to develop Covid-19 related complications including ARDS 109 (31.4%), heart failure 92 (26.5%), acute renal injury 17 (4.9%), and septic shock 14 (4.0%) compared with patients without co-morbidities (p-value < .001), (p-value < .001), (p-value = 0.004), and (p-value = 0.008) respectively. At the time of the last follow-up, 125 (24.3%) patients had died. Patients with at least one co-morbidity had a higher mortality percentage (32.0%) compared with patients without co-morbidities (8.3%) (p-value < .001). Patients who had surgery within the last month had higher reported Covid-19 related death 4 (30.8%) compared with all the other co-morbidities (Table 1).

Laboratory and Radiologic Findings

The most common chest CT findings were bilateral peripheral patchy consolidation 435 (84.5%) and ground-glass opacity 183 (35.5%). Laboratory tests revealed that the neutrophil count was significantly higher among patients with co-morbidities ($9.8 \pm 4.7 \times 10^9$/L) compared with patients without co-morbidities ($9.5 \pm 3.3 \times 10^9$/L), (p-value < .001). Patients in the co-morbidity group had a significantly lower lymphocyte count ($1.4 \pm 1.2 \times 10^9$/L) compared with patients without co-morbidities ($1.8 \pm 1.4 \times 10^9$/L) (p-value = 0.007). Higher levels of C-reactive protein (CRP) and D-dimer were found among patients with co-morbidities (82.0 ± 78.2mg/L and 1.9 ± 2.3mg/L) compared with patients without co-morbidities (36.7 ± 41.3mg/L and 1.1 ± 1.3mg/L), respectively, (p-value < .001). low platelet count, low hemoglobin levels, and high levels of aspartate aminotransferase (AST), Alanine Transaminase (ALT), creatinine, and blood urea were linked with Covid-19 patients with co-morbidities compared with patients without co-morbidities (p-value < .001) (Table 2).

Complications and outcomes of Covid-19 patients by types of co-morbidities

Comparing the outcomes of Covid-19 with different types of co-morbidities (hypertension, diabetes mellitus, cardiovascular diseases, COPD, malignancies, and obesity) showed that patients with malignancies were more vulnerable to poor outcomes including severe infection 22 (64.7%) and the need for mechanical ventilation 19 (55.9%) compared with other co-morbidities (p-value = 0.002) and (p-value = 0.001) respectively. Also, COPD patients were associated with severe complications 22 (62.9%), including ARDS 21 (60.0%), heart failure 19 (54.3%), and death 20 (57.1%) compared with other co-morbidities (p-value = 0.002), (p-value = 0.003), (p-value = 0.016), and (p-value = 0.018) (Table 3).

Multivariate Logistic Regression Analysis for factors associated with Severe Covid-19 infection in patients with co-morbidities

Multiple logistic regression analysis showed that patients ≥ 65 years old (vs. <65; OR: 2.344, p-value = .000), positive smoking history (vs. negative smoking history; OR: 1.786, p-value = 0.011), patients with ≥ 2 co-morbidities (vs. 1 co-morbidity; OR: 2.584, p-value = 0.004) and patients with COPD (vs. other co-morbidities; OR: 2.708, p-value = 0.011) were risk factors linked to severe Covid-19 infection in patients with co-morbidities. Diabetes mellitus patients (vs. other co-morbidities; OR: 1.235, p-value = 0.436) did not show significant differences (Figure 1D) (Table 4) (Supplementary Table 4).

Survival analysis

The Kaplan-Meier curve revealed that Covid-19 patients with at least one co-morbidity have significantly lower OS time compared to Covid-19 patients without co-morbidities [mean= 19.7 (18.6-20.8) vs. 27.1 (26.1-28.0), p-value < .000] (Figure 1A, Supplementary Table 1). Furthermore, patients with ≥ 2 co-morbidities (vs. one co-morbidity), patients with hypertension (vs. other co-morbidities), malignancies (vs. other co-morbidities), and obesity (vs. other co-morbidities) were found to have significantly shorter overall survival periods (Figure 1: B, C, E, F, and G) (Supplementary Tables: 2, 3, 5, 6, and 7). Diabetes mellitus patients (vs. other co-morbidities) did not show a significant difference (Figure 1D) (Supplementary Table 4).

Discussion:

This first study describes the impacts co-morbidities have on the infection severity among Syrian patients with Covid-19. In our study, we found that chronic disease was more prevalent with increasing age. Previous studies have proved the relationship between aging and chronic diseases.[21] [22]

Positive smoking history was linked to patients with co-morbidities compared with those without co-morbidities. Several studies found that tobacco is a well-known risk factor for early morbidity and mortality worldwide.[23] [24] Regarding vital signs on admission, patients with co-morbidities had a significantly higher mean temperature, heart rate, systolic blood pressure, and diastolic blood pressure than those without co-morbidities. This finding was consistent with a previous study conducted in China.[25] Considering Covid-19 clinical manifestations, the most common symptoms among all Covid-19 patients were dry cough, followed by weakness and fatigue, fever, and dyspnea. This was similar to other studies reported by the Sakarya University Training and Research Hospital, the European Centre for Disease Prevention and Control, and a systematic review.[26] [27] [28] Weakness and fatigue were the most frequent clinical presentation of Covid-19 infection in patients without co-morbidities. This was in line with a previous study from Turkey [29], where dyspnea was found to be the most common symptom among patients with co-morbidities in Egypt.[30] Dyspnea was linked to patients with co-morbidities compared with those without co-morbidities. This was consistent with a study conducted in Bangladesh.[31] Regarding Disease Severity, patients without co-morbidities were more likely to experience mild disease and this was reported by previous studies in China and Nigeria.[32] [33] On the other hand, severe cases were related to patients with co-morbidities and this was consistent with a study conducted in China and a literature review.[34] [35] The need for mechanical ventilation was linked to patients with co-morbidities. A previous study from the United States revealed a similar finding.[36]

We found that patients with pre-existing co-morbidities are more likely to suffer from Covid-19 complications and have a high mortality rate compared to those without co-morbidities. According to the Centers for Disease Control and Prevention (CDC), a person with one or more chronic medical conditions is more likely to experience severe Covid-19 infection and have poor outcomes.[37] Several studies have linked poor Covid-19 outcomes, including complications, and higher mortality rates with the presence of pre-existing chronic diseases.[38] [39] [40] [41] Regarding laboratory findings

higher neutrophil count, blood urea, creatinine, ALT, AST, CRP, and D-dimer levels, and lower haemoglobin levels, platelets count, and lymphocyte count were linked to patients with co-morbidities. A study conducted at the Memorial Healthcare System showed that patients with lymphocytopenia had a significantly higher co-morbidity profile compared with those without lymphocytopenia.[42] Previous studies revealed that co-morbidities were more frequent among patients with elevated D-dimer and CRP levels.[43] [44] Another study from China demonstrated that the blood levels of leukocyte count and neutrophil count and the serum concentrations of CRP were higher in patients with increased leukocyte count and chronic diseases.[45] It is recognized that patients with underlying chronic disease experience chronic systemic inflammation in their body and express more angiotensin-converting enzyme 2.[46] These may induce a higher systemic inflammatory response when infected with Covid-19 compared with patients without an underlying chronic disease. A lower haemoglobin level in hospitalized patients with Covid-19 was linked to the presence of underlying chronic diseases according to an Iranian study.[47] Hypertension followed by diabetes mellitus and cardiovascular disease were the most common co-morbidities in this study. Similar frequencies were reported in an Italian study and a Spanish study.[48] [49] Data showed recent surgery within one month before Covid-19 infection was linked to higher disease severity and mortality. A cohort study in Italy reported that mortality following surgery was significantly higher for those with Covid-19 infection compared with control patients without Covid-19.[50] The reason may be the overreaction of the immune system as a result of aggressive inflammatory response and release of excessive pro-inflammatory cytokines "cytokines storm", leading to multi-organ failure and effects on endothelial cells resulting in clot formation and infarctions.[51] [52] This interaction between the virus and the immune system could clarify the deterioration of the post-operative course, furthermore, most of this study's participants are elderly patients with underlying chronic diseases, which may add additional risk to postoperative morbidity and mortality. Covid-19 patients with a history of underlying malignancy were significantly associated with severe disease and the need for mechanical ventilation compared with other types of co-morbidities. A previous study conducted by the same authors showed that cancer patients are at high risk for severe complications and mortality due to Covid-19.[53] Systematic reviews showed the same results.[54] [55] [56] This present study suggested that ARDS and heart failure were more likely to occur among Covid-19 patients with COPD, in addition, they had the highest mortality in comparison with other types of co-morbidities. The significant impact COPD has on Covid-19 infected patients has been observed in systematic reviews and

retrospective studies.[57] [58] [59] [60] [61] A study from China suggested that Covid-19 infected patients with pre-existing COPD are more vulnerable to acute exacerbations of COPD and subsequent respiratory failure, which is the main culprit for unfavorable clinical outcomes.[62] Covid-19 uses the angiotensin-converting enzyme II (ACE2) as the cellular entry receptor.[63] A previous study showed that ACE2 expression on the epithelial cells in the lower airways was significantly higher among COPD versus non-COPD subjects. This can explain the increased risk of severe Covid-19 in this population.[64] Furthermore, this study revealed that elderly patients ≥ 65 years old, patients with positive smoking history, patients with two or more Co-morbidities, and patients with COPD had greater odds of experiencing severe Covid-19 infection. Several studies from China and Australia and 2 systematic reviews reported the same factors.[4] [65] [66] [67] This study showed that the overall survival time of Covid-19 patients with co-morbidities was lower than that in patients without co-morbidities. A retrospective cohort study reported that the presence of co-morbidities among hospitalized Covid-19 patients would reduce the survival rate among these patients.[68] Furthermore, the overall survival time was lower among patients with 2 or more co-morbidities compared to patients with only one co-morbidity. Other previous studies illustrated that a history of multiple co-morbidities was linked to an increase in the risk of death rate among Covid-19 patients.[69] [61] [63] This current study revealed that hypertension, obesity, malignancy, and COPD were related to a lower survival rate among Covid-19 patients. A study reported a lower probability of survival time among the hypertensive group compared with the non-hypertensive group.[70] Another study in Nigeria demonstrated that the risk of death was a 4-fold increase among the hypertensive group compared to the normotensive group.[71] A previous systematic review reported a high mortality rate was evident among obese patients admitted with Covid-19 compared with non-obese patients admitted with Covid-19.[72] [73] A multicenter retrospective study conducted in Syria by the same authors reported that cancer patients infected with Covid-19 receiving anticancer treatment had a lower overall survival.[53] Patients with diabetes mellitus did not show significant differences in OS when compared with other co-morbidities. A previous study in Bangladesh found the same result.[74] However, many other studies linked Covid-19 patients with diabetes to a significantly lower OS.[75] [76]

Limitations:

The main limitation of the study is the issues encountered with data collection, including disorganized files, subjective records, and illegible handwriting. To mitigate these issues patients were contacted for completion of data collection. Additionally, the system would benefit from electronic files for easier access and storage to eradicate most of the current study's flaws. Another limitation is the possibility of lost records, and the withdrawal of some patients, who were transferred to another hospital or private hospital for management. Conducting a prospective multicentre study on a national level should be the next step in overcoming these problems and providing better evidence.

Conclusion:

This retrospective observational study showed that patients with Covid-19 patients with co-morbidities were correlated with poor Covid-19 outcomes, including severe infection, need for ventilation support, higher mortality, and lower overall survival time. Therefore, patients with co-morbidities are highly vulnerable and must be protected against the virus. Patients with co-morbidities, who are eligible for the Covid-19 vaccine, must be encouraged to sign up and receive the Covid-19 vaccine along with the booster dose every 6 months.

Abbreviations: COVID-19: Coronavirus Disease 2019; FDA: Food and Drug Administration; OS: Overall Survival time; CDC: Centers for Disease Control and Prevention; RT-PCR: Reverse Transcription-Polymerase Chain Reaction; CRP: C-Reactive Protein; COPD: Chronic Obstructive Pulmonary Disease; CT: Computed Tomography; ARDS: Acute Respiratory Distress Syndrome; SPSS: statistical package for social sciences; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; CDC: Centers for Disease Control and Prevention; ACE2: Angiotensin-Converting Enzyme II.

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Availability of data and material:

The dataset(s) supporting the conclusions of this article are included within the article.

Declarations:

Ethical Approval and consent to participate

This study was approved by the Institutional Review Board (IRB) at the Syrian Private University (SPU). The IRB at SPU did not provide us with a number/ID. All Participants confirmed their written consent by answering a yes-no question. Participation in the study was voluntary and participants were assured that anyone who was not inclined to participate or decided to withdraw after giving consent would not be victimized. All information collected from this study was kept strictly confidential.

Consent for publication:

Not applicable.

Competing interests:

The authors declare none.

Authors' contributions:

MN and SA conceptualized the study, participated in the design, participated in data collection, wrote the study protocol, performed the statistical analysis, interpreted the results, did a literature search, and drafted the manuscript. MF

participated in data collection, participated in data encoding, and designed the figures. AA and YA participated in data collection. FM revised the final draft of the paper. All authors read and approved the final draft.

Tables:

Table 1. Socio-demographic features clinical manifestations, complications, and outcomes of Covid-19 patients with and without Co-morbidities.

	All patients (N= 515)	**Patients with co-morbidities (n=347)**	**Patients without co-morbidities (n= 168)**	**p-value**
Age (years)	60.2±14.6	63.9±14.4	52.7±12.2	0.004
Sex				
Male	316(61.4)	210(60.5)	106(63.1)	0.573
Female	199(38.6)	137(39.5)	62(36.9)	
Smoking history	192(37.3)	141(40.6)	51(30.4)	0.024
Vital signs on admission				
Temperature on admission (°C)	38.0±0.9	38.0±0.9	37.9±0.7	0.009
Heart rate (beats/ minute)	94.2±16.4	94.5±17.6	93.6±13.3	< .001
Respiratory rate (breath/ minute)	27.8±6.9	28.2±6.7	26.9±7.1	0.663
Systolic pressure (mmHg)	124.2±19.1	124.3±21.2	124.1±13.7	< .001
Diastolic pressure (mmHg)	75.7±12.3	76.1±13.6	74.9±8.9	< .001
Clinical manifestation				
Dry cough	380(73.8)	250(72.0)	130(77.4)	0.197
Dyspnea	357(69.3)	267(76.9)	90(53.6)	< .001
Fever	357(69.3)	242(69.7)	115(68.5)	0.766
Chills	119(23.1)	80(23.1)	39(23.2)	0.968
Weakness and fatigue	374(72.6)	242(69.7)	132(78.6)	0.035

Oedema	11(2.1)	11(3.2)	0(0.0)	0.020
Sore throat	73(14.2)	37(10.7)	36(21.4)	0.001
Chest pain	66(12.8)	52(15.0)	14(8.3)	0.034
Headache	115(22.3)	63(18.2)	52(31.6)	0.001
Runny nose	71(13.8)	24(6.9)	47(28.0)	< .001
Anosmia (loss of smell)	36(7.0)	18(5.2)	18(10.7)	0.021
Ageusia (loss of taste)	34(6.6)	16(4.6)	18(10.7)	0.009
Arthralgia	122(23.7)	70(20.2)	52(31.0)	0.007
Myalgia	137(26.6)	76(21.9)	61(36.3)	0.001
Irritability	9(1.7)	6(1.7)	3(1.8)	0.963
Confusion	52(10.1)	46(13.3)	6(3.6)	0.001
Loss of consciousness	24(4.7)	19(5.5)	5(3.0)	0.207
Nausea	29(5.6)	21(6.1)	8(4.8)	0.552
Vomiting	65(12.6)	43(12.4)	22(13.1)	0.822
Diarrhea	58(11.3)	40(11.5)	18(10.7)	0.784
Abdominal pain	33(6.4)	22(6.3)	11(6.5)	0.928
Lethargy	33(6.4)	28(8.1)	5(3.0)	0.027
bradyglossia	13(2.5)	12(3.5)	1(0.6)	0.052
Anorexia	103(20.0)	64(18.4)	39(23.2)	0.204
Loss of weight	21(4.1)	10(2.9)	11(6.5)	0.049
Disease severity				
Mild	185(35.9)	87(25.1)	98(58.3)	< .001
Moderate	203(39.4)	149(42.9)	54(32.1)	0.019
Severe	127(24.6)	111(32.0)	16(9.5)	< .001
Oxygen therapy	457(88.7)	306(88.2)	151(89.9)	0.568
Mechanical ventilation	113(21.9)	100(28.8)	13(7.7)	< .001
Complications	136(26.4)	120(34.6)	16(9.5)	< .001
ARDS	124(24.1)	109(31.4)	15(8.9)	< .001
Heart failure	103(20.0)	92(26.5)	11(6.5)	< .001
Acute renal injury	17(3.3)	17(4.9)	0(0)	0.004
Acute liver injury	4(0.8)	4(1.2)	0(0)	0.162

Septic shock	14(2.7)	14(4.0)	0(0)	0.008
Outcomes				
Alive at the time of last follow-up	390(75.7)	236(68.0)	154(91.7)	< .001
Death	125(24.3)	111(32.0)	12(8.3)	

Table 2. Comparison of laboratory findings between patients with co-morbidities and patients without co-morbidities

	All patients (N=515)	**Patients with co-morbidities (n=347)**	**Patients without co-morbidities (n=168)**	**p-value**
Leukocyte count (10^9/L)	11.5±4.7	11.6±5.2	11.5±3.6	< .001
Neutrophil count (10^9/L)	9.7±4.3	9.8±4.7	9.5±3.3	< .001
Lymphocyte count	1.5±1.2	1.4±1.2	1.8±1.4	0.007
Hemoglobin(gm/dL)	12.1±2.5	11.7±2.7	12.9±1.7	< .001
Platelets (10^9/L)	246.3±95.8	229.7±100.1	280.7±755.2	< .001
Alt (U/L)	27.2±15.4	28.2±17.2	24.6±10.8	< .001
Ast (U/L)	34.0±17.6	37.3±19.3	27.2±10.4	< .001
Creatinine (mg/dL)	1.6±1.4	1.9±1.6	1.2±0.4	< .001
Blood urea (mg/dL)	66.3±59.7	78.4±68.2	41.4±19.4	< .001
CRP (mg/L)	67.2±71.6	82.0±78.2	36.7±41.3	< .001
D-dimer (mg/L)	1.6±2.0	1.9±2.3	1.1±1.3	< .001

Table 3. Complications and outcomes of covid-19 patients by types of co-morbidities

	Hypertension (N=196)	**Diabetes mellitus (N=149)**	**Cardiovascular diseases (N=102)**	**COPD (N=35)**	**Malignancies (N=34)**	**Obesity (N=42)**	**P value**
Severe infection	68(34.7)	53(35.6)	36(35.3)	20(57.1)	22(64.7)	20(47.6)	0.002
Complications	76(38.8)	54(36.2)	39(38.2)	22(62.9)	19(55.9)	26(61.9)	0.002
ARDS	69(35.2)	50(33.6)	34(33.3)	21(60.0)	19(55.9)	22(52.4)	0.003
Heart failure	60(30.6)	43(28.9)	30(29.4)	19(54.3)	13(38.2)	20(47.6)	0.016
Acute renal injury	12(6.1)	8(5.4)	2(2.0)	3(8.6)	3(8.8)	0(0.0)	0.242

Acute liver injury	1(0.5)	1(0.7)	1(1.0)	0(0.0)	1(2.9)	0(0.0)	0.678
Septic shock	8(4.1)	5(3.4)	5(4.9)	2(5.7)	3(8.8)	5(11.9)	0.263
Mechanical ventilation	62(31.6)	44(29.5)	32(31.4)	18(51.4)	19(55.9)	23(54.8)	0.001
Outcomes							
Death	73(37.2)	54(36.2)	37(36.3)	20(57.1)	19(55.9)	23(54.8)	0.018

Table 4. Multivariable logistic regression analysis on risk factors associated with severe covid-19 infection in patients with Co-morbidities

	Odds Ratio	**95% C.I. for OR Lower**	**Upper**	**p-value**
≥65 years old (vs. < 65)	2.344	1.480	3.713	< .001
male (vs. female)	0.938	0.593	1.482	0.782
Positive smoking History (vs. negative History)	1.786	1.142	2.795	0.011
≥2 co-morbidities (vs. 1 co-morbidity)	2.584	1.364	4.897	0.004
Hypertension (vs. diabetes mellitus, cardiovascular diseases, COPD, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month)	0.782	0.426	1.433	0.426
Diabetes (vs. hypertension, cardiovascular diseases, COPD, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month)	1.235	0.726	2.101	0.436
COPD (vs. hypertension, diabetes mellitus, cardiovascular diseases, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month)	2.708	1.258	5.829	0.011

Figure legends:

Figure 1. Kaplan-Meier plot of OS comparing Covid-19 patients by co-morbidities.

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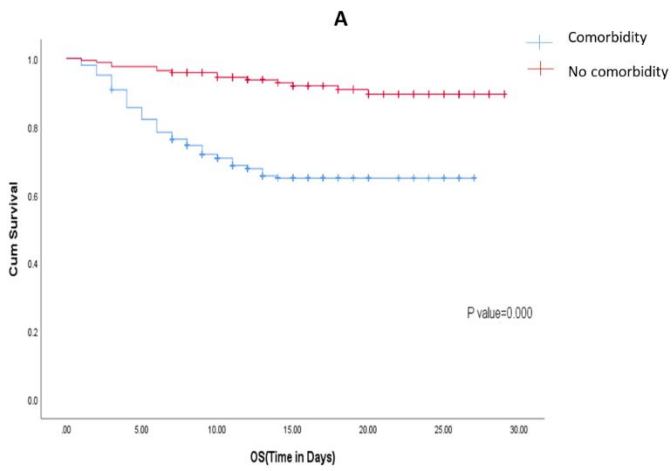

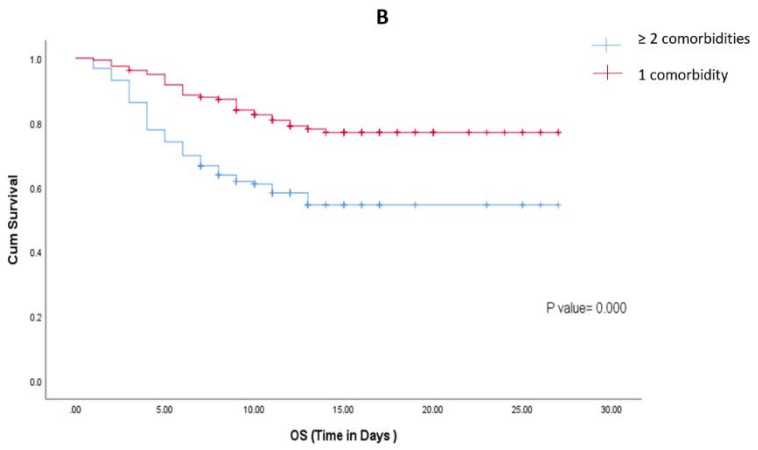

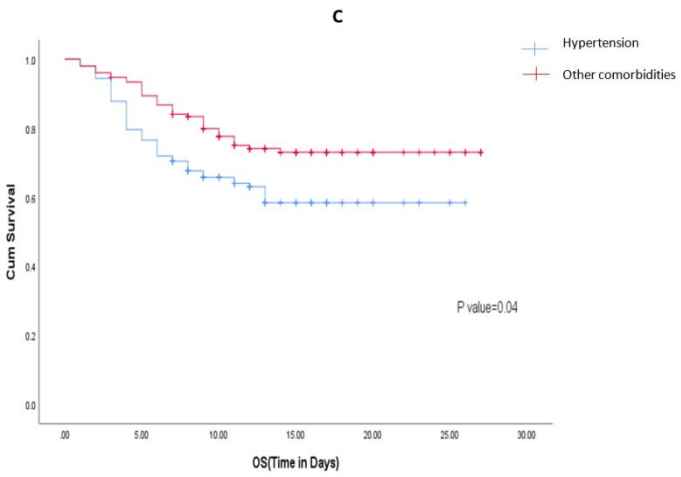

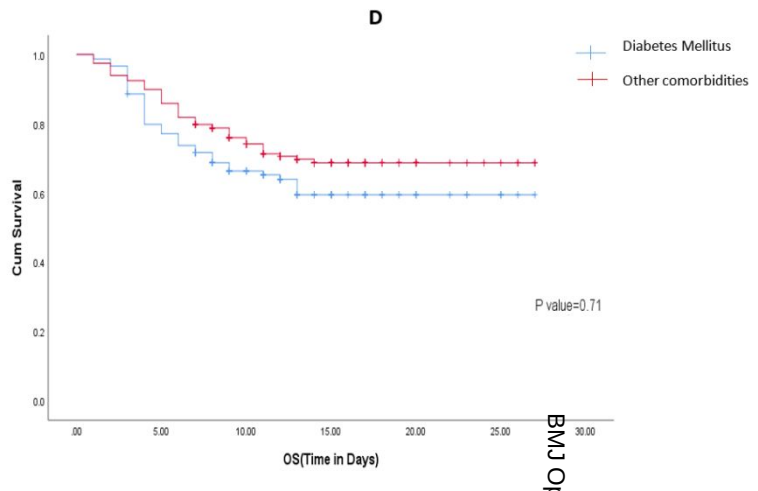

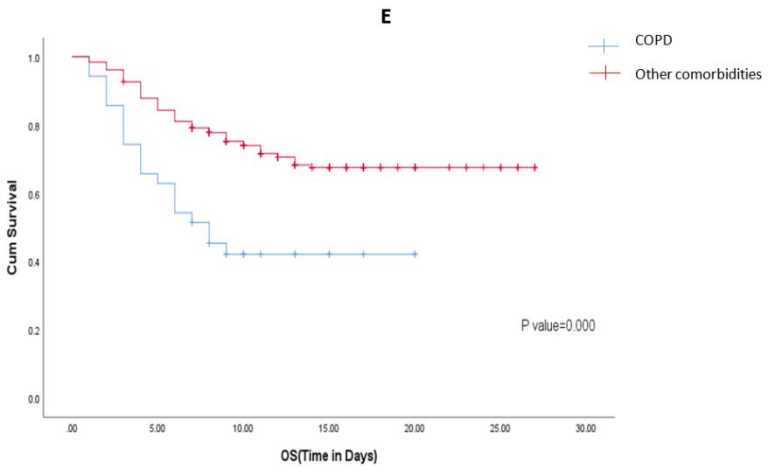

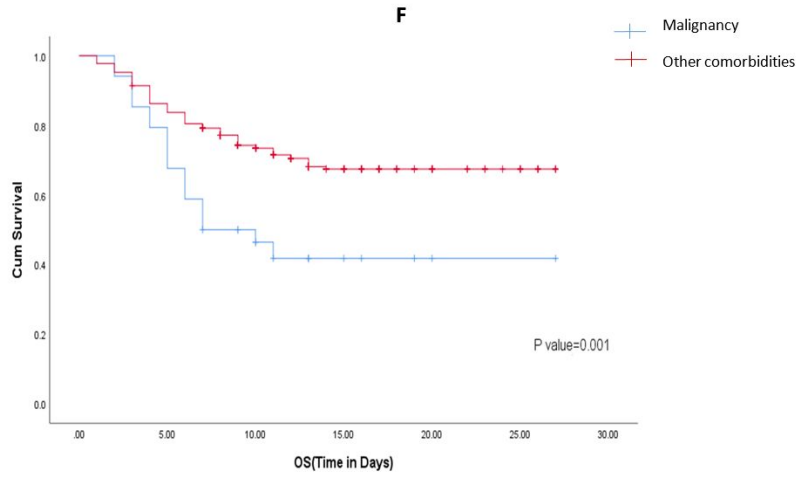

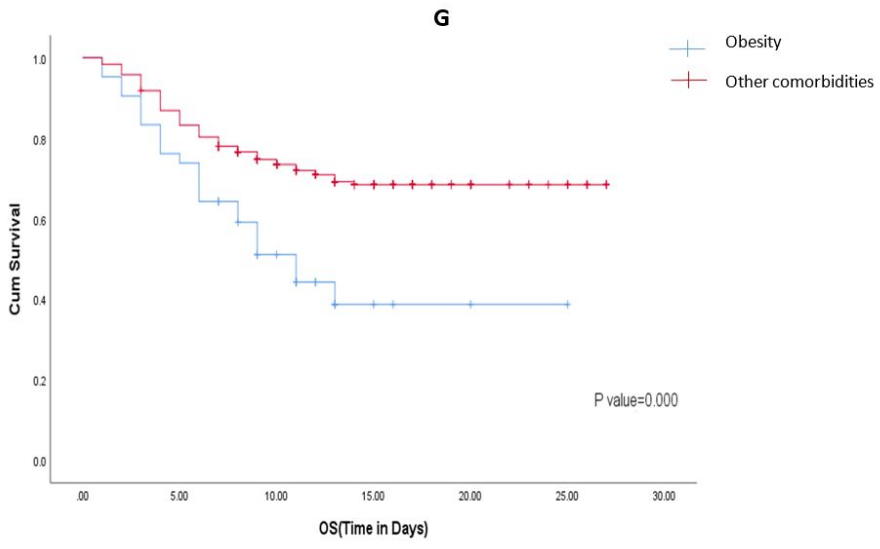

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	7-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-12

		(*b*) Report category boundaries when continuous variables were categorized	7-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The Impact of Co-morbidities on Hospitalized Syrian Patients with Covid-19- a Retrospective Study

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Abstract:

Objectives

This study aims to compare the clinical manifestations, laboratory findings, outcomes, and overall survival time of Covid-19 patients with and without co-morbidities.

Design

Retrospective design.

Setting

This study was undertaken at two hospitals in Damascus.

Participants

A total of 515 Syrian patients met the inclusion criteria, laboratory-confirmed Covid-19 infection following the Centers for Disease Control and Prevention. Exclusion criteria were suspected and probable cases that were not confirmed with a positive reverse transcription-polymerase chain reaction assay; and patients who self-discharged from the hospital against medical advice.

Primary and secondary outcome measures

First, assess the impacts of co-morbidities with Covid-19 infection in 4 areas (clinical manifestations, laboratory findings, and outcomes). Second, calculate the overall survival time for Covid-19 patients with co-morbidities.

Results

Of 515 patients included, 316 (61.4%) were male, and 347 (67.4%) had at least one coexisting chronic disease. Patients with co-morbidities compared with no co-morbidities were more vulnerable to poor outcomes such as severe infection (32.0% vs. 9.5%, p-value < .001), severe complications (34.6% vs. 9.5%, p-value < .001), the need for mechanical ventilation (28.8% vs. 7.7%, p-value < .001), and death (32.0% vs. 8.3%, p-value < .001). Multiple logistic regression showed that patients ≥ 65 years old, positive smoking history, patients with ≥ 2 co-morbidities, and patients with chronic obstructive pulmonary disease were risk factors linked to severe Covid-19 infection in patients with co-morbidities. Overall survival time was lower among patients with co-morbidities (vs. no co-morbidities), patients with ≥ 2 co-morbidities (vs. one co-morbidity), patients with hypertension, chronic obstructive pulmonary disease, malignancy, or obesity (vs. other co-morbidities) (p-value < 0.05).

Conclusion

This study revealed that covid-19 infection had poor outcomes among those with co-morbidities. Severe complications, mechanical ventilation usage, and death were more abundant among patients with co-morbidities compared to no co-morbidities.

Strengths and limitations of this study:

. Data collection issues include disorganized files, subjective records, lost records, and illegible handwriting.

. Data gathered included co-morbidities, clinical manifestations, laboratory findings, and outcomes of hospitalized Covid-19 patients.

. The retrospective design of the study is inferior in evidence compared with prospective studies.

. This study's sample covered two main Hospitals in Damascus and Rural-Damascus

. The ethics committee of Damascus Hospital granted the study's approval.

Keywords: Syrian Arab Republic, SARS-CoV-2, War, Conflict, Morbidity, Al-Mujtahid Hospital; Al- Mouwasat Hospital.

Introduction:

Since Coronavirus Disease 2019 (Covid-19) was first recognized in December 2019,[1] a collaborative effort focused on understanding the epidemiological, demographic, and clinical features of this virus was triggered. Covid-19 continues to spread, infecting over half a billion and killing millions.[2] Despite the thousands of published medical research and the milestones, we have overcome, the virus continues to cause unpredictable chaos.[3] One observation quickly noticed by the medical community after the start of the epidemic was that Covid-19 affects people differently, with most cases showing mild symptoms; however, many studies revealed that the presence of co-morbidities can be associated with more

severe infection cases and clinical complications.[4-6]Approximately one in five individuals is at increased risk of severe Covid-19.[7] After these results were announced around the world, it is not surprising that generalized anxiety and Covid-19-related fear were elevated among individuals with high-risk diseases such as diabetes, hypertension, cardiovascular, and chronic respiratory diseases.[8] In light of this crisis, the medical community has agreed that vaccines remain the only way to fight the pandemic, and in December 2020 the United States Food and Drug Administration (FDA) issued an emergency use authorization to facilitate the use and availability of Covid-19 vaccines.[9] Despite the conformation about the efficacy and safety of Covid-19 vaccines,[10, 11] vaccine hesitancy worldwide became a big obstacle in the vaccination process.[12] In Syria, only 9.3% of the population is fully vaccinated,[13] with vaccine hesitancy higher among people with a history of chronic co-morbidities.[14] Many studies showed that people with co-morbidities had greater odds of developing severe post-vaccination side effects.[15, 16] To accurately study the impact of co-morbidities on the severity of Covid-19 infection and thus confirm the importance of protecting this vulnerable group, this study was conducted to evaluate the impact of co-morbidities on the clinical manifestations, laboratory findings, and outcomes of Covid-19 infected patients. The objective was to study the differences in outcomes and overall survival time (OS) between Covid-19 patients with different types of co-morbidities.

Methods:

Study Design, settings, and participants

This retrospective, multicenter, observational study was conducted at two main Hospitals in Damascus and Rural-Damascus, Damascus Hospital (Al-Mujtahid) and Al- Mouwasat Hospital. Al-Mouwasat Hospital is affiliated with the Syrian Ministry of higher education and scientific research. Damascus Hospital is affiliated with the Syrian Ministry of health. Damascus Hospital and Al-Mouwasat Hospital were emergency hospitals involved in the isolation and management of patients with Covid-19 during the outbreaks. A total of 515 patients with confirmed Covid-19 diagnoses between 1/9/2021 and 30/9/2021 were enrolled in this study. The third Covid-19 wave peaked in September 2021.

Inclusion criteria

Inclusion criteria were Damascus hospital laboratory and Al- Mouwasat Hospital laboratory- confirmed Covid-19

infection following the Centers for Disease Control and Prevention (CDC) published criteria.[17, 18]

Exclusion criteria

Exclusion criteria were suspected and probable cases that were not confirmed with a positive reverse transcription-polymerase chain reaction (RT-PCR) assay; and patients who self-discharged from the hospital against medical advice, and therefore, missed their outpatient follow-up.

Data collection

Clinical records and laboratory results were reviewed by the authors. Furthermore, the authors contacted patients via telephone when data from files were incomplete. The data collected included socio-demographic features: age, sex, and smoking history; vital signs: temperature, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure; clinical symptoms: dry cough, dyspnea, fever, chills, weakness and fatigue, oedema, sore throat, chest pain, headache, runny nose, anosmia, ageusia, arthralgia, myalgia, irritability, confusion, loss of consciousness, nausea, vomiting, diarrhea, abdominal pain, lethargy, bradyglossia, anorexia, and weight loss; co-morbidities: hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month; complications: acute respiratory distress syndrome (ARDS), heart failure, acute renal injury, cute liver injury, and septic shock; laboratory results on admission: complete blood count, kidney function tests, liver function tests, D-dimer, and C-reactive protein (CRP); radiological assessment; RT-PCR results; clinical outcomes: complete recovery, need for oxygen therapy, need for mechanical ventilation, and death.

Two investigators separately checked the data collection to confirm the accuracy of the data gathered. Patients were classified into two groups, the first group, Covid-19 patients with at least one of the following co-morbidities, hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month; the second group, Covid-19 patients without any co-morbidity.

Ethical Approval

This study was approved by the ethics committee of Damascus Hospital, Syrian Ministry of Health. This study was not granted a specific identification number.

Study Definitions

Manifestations found on chest x-ray and computed tomography (CT) scans were reviewed by an attending physician in the Respiratory department. ARDS was diagnosed when someone with a confirmed Covid-19 infection met the Berlin 2012 ARDS diagnostic criteria: 1) acute hypoxemic respiratory failure 2) presentation within 1 week of worsening respiratory symptoms 3) bilateral airspace disease on chest x-ray, CT, or ultrasound that is not fully explained by effusions, labor or lung collapse, or nodules 4) cardiac failure is not the primary cause of acute hypoxemic respiratory failure.[19] Covid-19 infection severity was divided into three groups: mild, moderate, and severe based on the National Institutes of Health Covid-19 treatment guidelines.[20]

Patient and public involvement

The public was not involved in the study design, conduct of the study, or plans to disseminate the results to study participants.

Statistical Analysis

Categorical variables were reported as frequencies and percentages (descriptive Statistics), and continuous variables were presented as medians with inter-quartile ranges (IQR). The Mann-Whitney U test was conducted to compare the age, vital signs on admission and laboratory results between Covid-19 patients with co-morbidities and Covid-19 patients without co-morbidities. The chi-square test and Fisher's exact test were used as appropriate to compare 2 groups, Covid-19 patients with co-morbidities and Covid-19 patients without co-morbidities, against socio-demographic features, clinical manifestations, complications, and outcomes. The chi-square test was also used to compare Covid-19 patients with different co-morbidities (hypertension, diabetes mellitus, cardiovascular disease, COPD, malignancy, and obesity) against severe infection, complications (ARDS, heart failure, acute renal injury, acute kidney injury, and septic shock), mechanical ventilation, and death. Multivariable logistic regression was performed to detect factors associated with severe Covid-19 infection (vs. no severe Covid-19 infection), selected factors included age (≥ 65 years vs. < 65 years), sex (male

vs. female), smoking history (positive smoking history vs. negative smoking history), number of co-morbidities (≥ 2 co-morbidities vs. one co-morbidity), and type of co-morbidities (hypertension vs. diabetes mellitus, cardiovascular diseases, COPD, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month), (diabetes vs. hypertension, cardiovascular diseases, COPD, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month), and (COPD vs. hypertension, diabetes mellitus, cardiovascular diseases, chronic, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month). For survival analysis, the set time from the presence of symptoms until death or the last follow-up (30 September 2021) was used. The Kaplan-Meier survival curves were conducted and differences in survival rate were analyzed by log-rank test. All statistical analyses were performed using the statistical package for social sciences (SPSS) statistics version 25.0. A statistically significant p-value was set at < 0.05.

Results:

Socio-demographic features clinical manifestations, complications, and outcomes of Covid-19 Patients

A total of 515 patients with Covid-19 were included in this study. The median age was 60 years, and the range was between 16 and 95 years. Males represented 316 (61.4%) and females represented 199 (38.6%). 192 (37.3%) patients were current or previous smokers. Of 347 (67.4%) patients with co-morbidities, 196 (56.6%) have hypertension, 149 (42.9%) have diabetes mellitus, 102 (29.4%) have a cardiovascular disease,43 (12.4%) have a renal disease, 42 (12.1%) are obese, 35 (10.1%) have COPD, 34 (9.8%) have malignancies, 29 (8.4%) have a neurological disease, 23 (6.6%) have an autoimmune disease, 14 (4.0%) have a hematological disease, 13 (3.7%) have a gastrointestinal and liver disease, and 13 (3.7%) had surgery within the last month. 189 (36.7%) reported having two or more co-morbidities. The median (IQR) number of co-morbidities for the population was 1(2) comorbidity, ranging from 0 to 7 comorbidities. Patients with co-morbidities were older (median = 65 years) compared with patients with no co-morbidities (median = 52 years). Also, patients with co-morbidities had a higher positive smoking history (40.6%) compared with no co-morbidities (30.4%).

Patients with co-morbidities had higher respiratory rate on admission (median=28 breath/minute) in comparison with patients without co-morbidities (p-value = 0.009). The most common symptoms among Covid-19 patients were dry cough 380 (73.8%), weakness and fatigue 374 (72.6%), fever 357 (69.3%), and dyspnea 357 (69.3%). The predominant clinical presentation among Covid-19 patients with co-morbidities was dyspnea 267 (76.9%), followed by dry cough 250 (72.0%), fever 242 (69.7%), and weakness and fatigue 242 (69.7%). Whereas, weakness and fatigue 132 (78.6%) was the most common clinical symptom among Covid-19 patients without co-morbidities. Patients with co-morbidities were more likely to suffer from dyspnea (76.9%) compared with patients without co-morbidities (53.6%) (p-value < .001) (Table 1).

Regarding Covid-19 severity, most patients had moderate disease 203 (39.4%). Patients without co-morbidities were more likely to experience mild disease 98 (58.3%). 127 (24.6%) patients developed severe Covid-19, and severe infection was more common among patients with at least one co-morbidity 111 (32.0%) compared with those without co-morbidities 16 (9.5%) (p-value < .001). A comparison of Covid-19 infection severity between patients with different co-morbidities showed that patients who had surgery during the last month were more likely to develop severe infection 9 (69.2%), followed by patients with malignancies 22 (64.7%), and COPD 20 (57.1%). A total of 457 (88.7%) patients required oxygen support. Patients with co-morbidities were more vulnerable to poor outcomes including severe complications compared with patients without co-morbidities 34.6% and 9.5% respectively (p-value < .001). Patients with co-morbidities were associated with the need for mechanical ventilation (28.8%) compared with patients without co-morbidities (7.7%) (p-value < .001). Patients with co-morbidities were more likely to develop Covid-19 related complications including ARDS 109 (31.4%), heart failure 92 (26.5%), acute renal injury 17 (4.9%), and shock 14 (4.0%) compared with patients without co-morbidities (p-value < .001), (p-value < .001), (p-value = 0.002), and (p-value = 0.007) respectively. At the time of the last follow-up, 125 (24.3%) patients had died. Patients with at least one co-morbidity had a higher mortality percentage (32.0%) compared with patients without co-morbidities (8.3%) (p-value < .001). Patients who had surgery within the last month had higher reported Covid-19 related death 4 (30.8%) compared with all the other co-morbidities (Table 1).

Laboratory and Radiologic Findings

The most common chest CT findings were bilateral peripheral patchy consolidation 435 (84.5%) and ground-glass opacity 183 (35.5%). Laboratory tests revealed that patients in the co-morbidity group had a significantly lower lymphocyte count (1.0×10^9/L) compared with patients without co-morbidities (1.4×10^9/L) (p-value < .001). Higher levels of C-reactive protein (CRP) and D-dimer were found among patients with co-morbidities (55.1 mg/L and 0.8 µg/L) compared with patients without co-morbidities (24.0 mg/L and 0.6 mg/L), (p-value < .001) and (p-value= 0.05) respectively. low platelet count, low hemoglobin levels, and high levels of aspartate aminotransferase (AST), creatinine, and blood urea were linked with Covid-19 patients with co-morbidities compared with patients without co-morbidities (p-value < .001) (Table 2).

Complications and outcomes of Covid-19 patients by types of co-morbidities

Comparing the outcomes of Covid-19 with different types of co-morbidities (hypertension, diabetes mellitus, cardiovascular diseases, COPD, malignancies, and obesity) showed that patients with malignancies were more vulnerable to poor outcomes including severe infection 22 (64.7%) and need for mechanical ventilation 19 (55.9%) compared with other co-morbidities (p-value = 0.002) and (p-value = 0.001) respectively. Also, COPD patients were associated with severe complications 22 (62.9%), including ARDS 21 (60.0%), heart failure 19 (54.3%), and death 20 (57.1%) compared with other co-morbidities (p-value = 0.002), (p-value = 0.003), (p-value = 0.016), and (p-value = 0.018) (Table 3).

Multivariate Logistic Regression Analysis for factors associated with Severe Covid-19 infection in patients with co-morbidities

Multiple logistic regression analysis showed that patients ≥ 65 years old (vs. <65; OR: 2.344, p-value = .000), positive smoking history (vs. negative smoking history; OR: 1.786, p-value = 0.011), patients with ≥ 2 co-morbidities (vs. 1 co-morbidity; OR: 2.584, p-value = 0.004) and patients with COPD (vs. other co-morbidities; OR: 2.708, p-value = 0.011) were risk factors linked to severe Covid-19 infection in patients with co-morbidities. Diabetes mellitus patients (vs. other co-morbidities; OR: 1.235, p-value = 0.436) did not show significant differences (Table 4).

Survival analysis

The Kaplan-Meier curve revealed that Covid-19 patients with at least one co-morbidity have significantly lower OS time compared to Covid-19 patients without co-morbidities [mean= 19.7 (18.6-20.8) vs. 27.1 (26.1-28.0), p-value < .000] (Figure 1A, Supplementary Table 1). Furthermore, patients with ≥ 2 co-morbidities (vs. one co-morbidity), patients with hypertension (vs. other co-morbidities), malignancies (vs. other co-morbidities), and obesity (vs. other co-morbidities) were found to have significantly shorter overall survival periods (Figure 1: B, C, E, F, and G) (Supplementary Tables: 2, 3, 5, 6, and 7). Diabetes mellitus patients (vs. other co-morbidities) did not show a significant difference (Figure 1D) (Supplementary Table 4).

Discussion:

This first study describes the impacts co-morbidities have on the infection severity among Syrian patients with Covid-19. In our study, we found that chronic disease was more prevalent with increasing age. Previous studies have proved the relationship between aging and chronic diseases.[21, 22]

Positive smoking history was linked to patients with co-morbidities compared with those without co-morbidities. Several studies found that tobacco is a well-known risk factor for early morbidity and mortality worldwide.[23, 24]Regarding vital signs on admission, patients with co-morbidities had a significantly higher respiratory rate than those without co-morbidities. This finding was consistent with a previous study conducted in China.[25] Considering Covid-19 clinical manifestations, the most common symptoms among all Covid-19 patients were dry cough, followed by weakness and fatigue, fever, and dyspnea. This was similar to other studies reported by the Sakarya University Training and Research Hospital, the European Centre for Disease Prevention and Control, and a systematic review.[26-28] Weakness and fatigue were the most frequent clinical presentation of Covid-19 infection in patients without co-morbidities. This was in line with a previous study from Turkey [29], where dyspnea was found to be the most common symptom among patients with co-morbidities in Egypt.[30] Dyspnea was linked to patients with co-morbidities compared with those without co-morbidities. This was consistent with a study conducted in Bangladesh.[31] Regarding Disease Severity, patients without co-morbidities were more likely to experience mild disease and this was reported by previous studies in China and Nigeria.[32, 33]On the other hand, severe cases were related to patients with co-morbidities and this was consistent with a

study conducted in China and a literature review.[34, 35]The need for mechanical ventilation was linked to patients with co-morbidities. A previous study from the United States revealed a similar finding.[36]

We found that patients with pre-existing co-morbidities are more likely to suffer from Covid-19 complications and have a high mortality rate compared to those without co-morbidities. According to the Centers for Disease Control and Prevention (CDC), a person with one or more chronic medical conditions is more likely to experience severe Covid-19 infection and have poor outcomes.[37] Several studies have linked poor Covid-19 outcomes, including complications, and higher mortality rates with the presence of pre-existing chronic diseases.[38-41] Regarding laboratory findings significantly higher blood urea, creatinine, AST, CRP, and D-dimer levels, and lower haemoglobin levels, platelets count, and lymphocyte count were linked to patients with co-morbidities. A study conducted at the Memorial Healthcare System showed that patients with lymphocytopenia had a significantly higher co-morbidity profile compared with those without lymphocytopenia.[42] Previous studies revealed that co-morbidities were more frequent among patients with elevated D-dimer and CRP levels.[43, 44] Another study from China demonstrated that the blood levels of leukocyte count and neutrophil count and the serum concentrations of CRP were higher in patients with increased leukocyte count and chronic diseases.[45] It is recognized that patients with underlying chronic disease experience chronic systemic inflammation in their body and express more angiotensin-converting enzyme 2.[46] These may induce a higher systemic inflammatory response when infected with Covid-19 compared with patients without an underlying chronic disease. A lower haemoglobin level in hospitalized patients with Covid-19 was linked to the presence of underlying chronic diseases according to an Iranian study.[47] Hypertension followed by diabetes mellitus and cardiovascular disease were the most common co-morbidities in this study. Similar frequencies were reported in an Italian study and a Spanish study.[48, 49] Data showed recent surgery within one month before Covid-19 infection was linked to higher disease severity and mortality. A cohort study in Italy reported that mortality following surgery was significantly higher for those with Covid-19 infection compared with control patients without Covid-19.[50] The reason may be the overreaction of the immune system as a result of an aggressive inflammatory response and release of excessive pro-inflammatory cytokines "cytokines storm", leading to multi-organ failure and effects on endothelial cells resulting in clot formation and infarctions.[51, 52] This interaction between the virus and the immune system could clarify the deterioration of the post-operative course, furthermore, most of this study's participants are elderly patients with underlying chronic diseases,

which may add additional risk to postoperative morbidity and mortality. Covid-19 patients with a history of underlying malignancy were significantly associated with severe disease and the need for mechanical ventilation compared with other types of co-morbidities. A previous study conducted by the same authors showed that cancer patients are at high risk for severe complications and mortality due to Covid-19.[53] Systematic reviews showed the same results.[54-56] This present study suggested that ARDS and heart failure were more likely to occur among Covid-19 patients with COPD, in addition, they had the highest mortality in comparison with other types of co-morbidities. The significant impact COPD has on Covid-19 infected patients has been observed in systematic reviews and retrospective studies.[57-61] A study from China suggested that Covid-19 infected patients with pre-existing COPD are more vulnerable to acute exacerbations of COPD and subsequent respiratory failure, which is the main culprit for unfavorable clinical outcomes.[62] Covid-19 uses the angiotensin-converting enzyme II (ACE2) as the cellular entry receptor.[63] A previous study showed that ACE2 expression on the epithelial cells in the Lower airways was significantly higher among COPD versus non-COPD subjects. This can explain the increased risk of severe Covid-19 in this population.[64] Furthermore, this study revealed that elderly patients ≥ 65 years old, patients with positive smoking history, patients with two or more Co-morbidities, and patients with COPD had greater odds of experiencing severe Covid-19 infection. Several studies from China and Australia and 2 systematic reviews reported the same factors.[4, 65-67] This study showed that the overall survival time of Covid-19 patients with co-morbidities was lower than that of patients without co-morbidities. A retrospective cohort study reported that the presence of co-morbidities among hospitalized Covid-19 patients would reduce the survival rate among these patients.[68] Furthermore, the overall survival time was lower among patients with 2 or more co-morbidities compared to patients with one co-morbidity. Other previous studies illustrated that a history of multiple co-morbidities was linked to an increased death rate among Covid-19 patients.[61, 63, 69] This current study revealed that hypertension, obesity, malignancy, and COPD were related to a lower survival rate among Covid-19 patients. A study reported a lower probability of survival time among the hypertensive group compared with the non-hypertensive group.[70] Another study in Nigeria demonstrated that the risk of death was a 4-fold increase among the hypertensive group compared to the normotensive group.[71] A previous systematic review reported a high mortality rate was evident among obese patients admitted with Covid-19 compared with non-obese patients admitted with Covid-19.[72, 73] A multicenter retrospective study conducted in Syria by the same authors reported that cancer patients infected with Covid-19 receiving anticancer

treatment had a lower overall survival.[53] Patients with diabetes mellitus did not show significant differences in OS when compared with other co-morbidities. A previous study in Bangladesh found the same result.[74] However, many other studies linked Covid-19 patients with diabetes to a significantly lower OS.[75, 76]

Limitations:

The main limitation of the study is the issues encountered with data collection, including disorganized files, subjective records, and illegible handwriting. To mitigate these issues patients were contacted for the completion of data collection. Additionally, the system would benefit from electronic files for easier access and storage to eradicate most of the current study's flaws. Another limitation is the possibility of lost records, and the withdrawal of some patients, who were transferred to another hospital or private hospital for management. Conducting a prospective multicentre study on a national level should be the next step in overcoming these problems and providing better evidence.

Conclusion:

This retrospective observational study showed that patients with Covid-19 patients with co-morbidities were correlated with poor Covid-19 outcomes, including severe infection, need for ventilation support, higher mortality, and lower overall survival time. Therefore, patients with co-morbidities are highly vulnerable and must be protected against the virus. Patients with co-morbidities, who are eligible for the Covid-19 vaccine, must be encouraged to sign up and receive the Covid-19 vaccine.

Abbreviations: COVID-19: Coronavirus Disease 2019; FDA: Food and Drug Administration; OS: Overall Survival time; CDC: Centers for Disease Control and Prevention; RT-PCR: Reverse Transcription-Polymerase Chain Reaction; CRP: C-Reactive Protein; COPD: Chronic Obstructive Pulmonary Disease; CT: Computed Tomography; ARDS: Acute

Respiratory Distress Syndrome; SPSS: statistical package for social sciences; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; CDC: Centers for Disease Control and Prevention; ACE2: Angiotensin-Converting Enzyme II.

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Availability of data and material:

The dataset(s) supporting the conclusions of this article are included within the article.

Declarations:

Ethical Approval and consent to participate

This study was approved by the Institutional Review Board (IRB) at the Syrian Private University (SPU). The IRB at SPU did not provide us with a number/ID. All Participants confirmed their written consent by answering a yes-no question. Participation in the study was voluntary and participants were assured that anyone who was not inclined to participate or decided to withdraw after giving consent would not be victimized. All information collected from this study was kept strictly confidential.

Consent for publication:

Not applicable.

Competing interests:

The authors declare none.

Authors' contributions:

MN and SA conceptualized the study, participated in the design, participated in data collection, wrote the study protocol, performed the statistical analysis, interpreted the results, did a literature search, and drafted the manuscript. MF participated in data collection, participated in data encoding, and designed the figures. AA and YA participated in data collection. FM revised the final draft of the paper. All authors read and approved the final draft.

Table 1. Socio-demographic features clinical manifestations, complications, and outcomes of Covid-19 patients with and without Co-morbidities.

	All patients (N= 515)	**Patients with co-morbidities (n=347)**	**Patients without co-morbidities (n= 168)**	**p-value**
Age (years). Median(IQR)	60(21)	65(19)	52(12)	< .001
Sex				
Male	316(61.4)	210(60.5)	106(63.1)	0.573
Female	199(38.6)	137(39.5)	62(36.9)	
Smoking history	192(37.3)	141(40.6)	51(30.4)	0.024
Vital signs on admission. median (IQR)				
Temperature on admission (°C)	38(1)	38(1)	38(1)	0.989
Heart rate (beats/ minute)	94(21)	95(25)	93(16)	0.316
Respiratory rate (breath/ minute)	28(8)	28(10)	26(8)	0.009
Systolic pressure (mmHg)	120(29)	120(30)	123(10)	0.594
Diastolic pressure (mmHg)	80(10)	80(10)	77(10)	0.605
Clinical manifestation				
Dry cough	380(73.8)	250(72.0)	130(77.4)	0.197
Dyspnea	357(69.3)	267(76.9)	90(53.6)	< .001
Fever	357(69.3)	242(69.7)	115(68.5)	0.766
Chills	119(23.1)	80(23.1)	39(23.2)	0.968
Weakness and fatigue	374(72.6)	242(69.7)	132(78.6)	0.035
Oedema	11(2.1)	11(3.2)	0(0.0)	0.019
Sore throat	73(14.2)	37(10.7)	36(21.4)	0.001
Chest pain	66(12.8)	52(15.0)	14(8.3)	0.034
Headache	115(22.3)	63(18.2)	52(31.6)	0.001
Runny nose	71(13.8)	24(6.9)	47(28.0)	< .001

Anosmia (loss of smell)	36(7.0)	18(5.2)	18(10.7)	0.021
Ageusia (loss of taste)	34(6.6)	16(4.6)	18(10.7)	0.009
Arthralgia	122(23.7)	70(20.2)	52(31.0)	0.007
Myalgia	137(26.6)	76(21.9)	61(36.3)	0.001
Irritability	9(1.7)	6(1.7)	3(1.8)	1.000
Confusion	52(10.1)	46(13.3)	6(3.6)	0.001
Loss of consciousness	24(4.7)	19(5.5)	5(3.0)	0.207
Nausea	29(5.6)	21(6.1)	8(4.8)	0.552
Vomiting	65(12.6)	43(12.4)	22(13.1)	0.822
Diarrhea	58(11.3)	40(11.5)	18(10.7)	0.784
Abdominal pain	33(6.4)	22(6.3)	11(6.5)	0.928
Lethargy	33(6.4)	28(8.1)	5(3.0)	0.027
bradyglossia	13(2.5)	12(3.5)	1(0.6)	0.070
Anorexia	103(20.0)	64(18.4)	39(23.2)	0.204
Loss of weight	21(4.1)	10(2.9)	11(6.5)	0.049
Disease severity				
Mild	185(35.9)	87(25.1)	98(58.3)	< .001
Moderate	203(39.4)	149(42.9)	54(32.1)	0.019
Severe	127(24.6)	111(32.0)	16(9.5)	< .001
Oxygen therapy	457(88.7)	306(88.2)	151(89.9)	0.568
Mechanical ventilation	113(21.9)	100(28.8)	13(7.7)	< .001
Complications	136(26.4)	120(34.6)	16(9.5)	< .001
ARDS	124(24.1)	109(31.4)	15(8.9)	< .001
Heart failure	103(20.0)	92(26.5)	11(6.5)	< .001
Acute renal injury	17(3.3)	17(4.9)	0(0)	0.002
Acute liver injury	4(0.8)	4(1.2)	0(0)	0.309
Septic shock	14(2.7)	14(4.0)	0(0)	0.007
Outcomes				
Alive at the time of last follow-up	390(75.7)	236(68.0)	154(91.7)	< .001
Death	125(24.3)	111(32.0)	12(8.3)	

Table 2. Comparison of laboratory findings between patients with co-morbidities and patients without co-morbidities

Laboratory findings. Median(IQR)	All patients (N=515)	Patients with co-morbidities (n=347)	Patients without co-morbidities (n=168)	p-value
Leukocyte count (10^9/L)	11.4(7.0)	11.0(8.6)	11.8(4.8)	0.558
Neutrophil count (10^9/L)	9.1(6.2)	9.1(7.4)	9.3(4.3)	0.857
Lymphocyte count	1.1(1.3)	1.0(1.1)	1.4(1.6)	< .001
Hemoglobin(gm/dL)	12.7(3)	12.0(4)	13.1(2)	< .001
Platelets (10^9/L)	244(113)	220(125)	289(80)	< .001
Alt (U/L)	23(16)	23(17)	21(13)	0.110
Ast (U/L)	30(19)	33(20)	24(13)	< .001
Creatinine (mg/dL)	1.2(1)	1.3(1)	1.1(0)	< .001
Blood urea (mg/dL)	47(41)	57(52)	40(16)	< .001
CRP (mg/L)	44(59)	55.1(82)	24(19)	< .001
D-dimer (mg/L)	0.7(2)	0.8(3)	0.6(1)	0.05

Table 3. Complications and outcomes of covid-19 patients by types of co-morbidities

	Hypertension (N=196)	Diabetes mellitus (N=149)	Cardiovascular diseases (N=102)	COPD (N=35)	Malignancies (N=34)	Obesity (N=42)	P value
Severe infection	68(34.7)	53(35.6)	36(35.3)	20(57.1)	22(64.7)	20(47.6)	0.002
Complications	76(38.8)	54(36.2)	39(38.2)	22(62.9)	19(55.9)	26(61.9)	0.002
ARDS	69(35.2)	50(33.6)	34(33.3)	21(60.0)	19(55.9)	22(52.4)	0.003
Heart failure	60(30.6)	43(28.9)	30(29.4)	19(54.3)	13(38.2)	20(47.6)	0.016
Acute renal injury	12(6.1)	8(5.4)	2(2.0)	3(8.6)	3(8.8)	0(0.0)	0.242
Acute liver injury	1(0.5)	1(0.7)	1(1.0)	0(0.0)	1(2.9)	0(0.0)	0.678
Septic shock	8(4.1)	5(3.4)	5(4.9)	2(5.7)	3(8.8)	5(11.9)	0.263
Mechanical ventilation	62(31.6)	44(29.5)	32(31.4)	18(51.4)	19(55.9)	23(54.8)	0.001
Outcomes							

Death	73(37.2)	54(36.2)	37(36.3)	20(57.1)	19(55.9)	23(54.8)	0.018

*multiple test corrections were not applied.

Table 4. Multivariable logistic regression analysis on risk factors associated with severe covid-19 infection in patients with Co-morbidities

	Odds Ratio	**95% C.I. for OR Lower**	**Upper**	**p-value**
≥65 years old (vs. < 65)	2.344	1.480	3.713	< .001
male (vs. female)	0.938	0.593	1.482	0.782
Positive smoking History (vs. negative History)	1.786	1.142	2.795	0.011
≥2 co-morbidities (vs. 1 co-morbidity)	2.584	1.364	4.897	0.004
Hypertension (vs. diabetes mellitus, cardiovascular diseases, COPD, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month)	0.782	0.426	1.433	0.426
Diabetes (vs. hypertension, cardiovascular diseases, COPD, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month)	1.235	0.726	2.101	0.436
COPD (vs. hypertension, diabetes mellitus, cardiovascular diseases, chronic liver disease, chronic kidney disease, gastrointestinal disease, neurological disease, malignancy, autoimmune disease, obesity, and recent surgery within the last month)	2.708	1.258	5.829	0.011

*the accuracy rate for the model is 76.9%

Figure legends:

Figure 1. Kaplan-Meier plot of OS comparing Covid-19 patients by co-morbidities.

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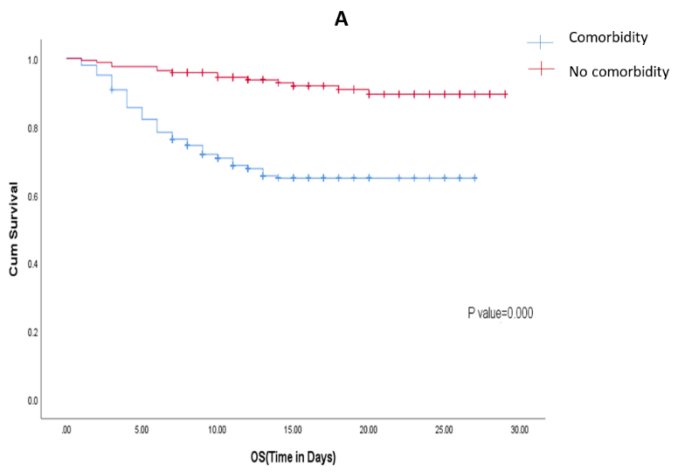

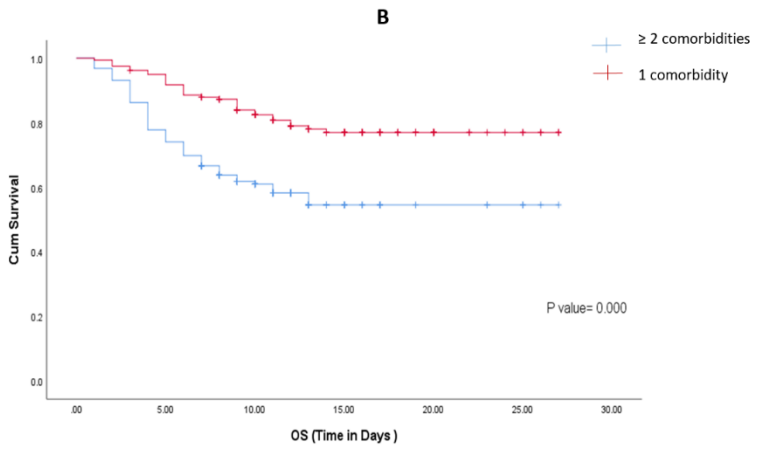

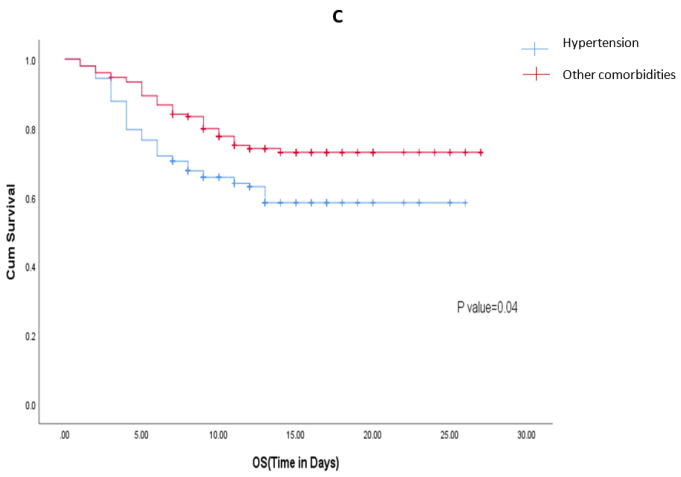

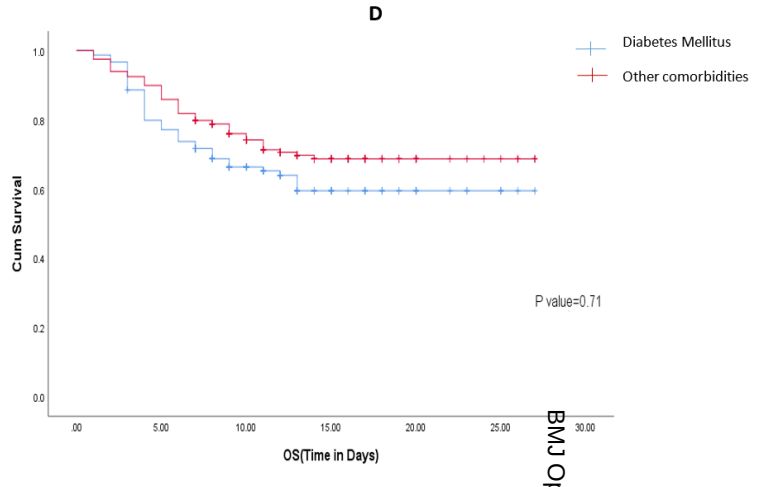

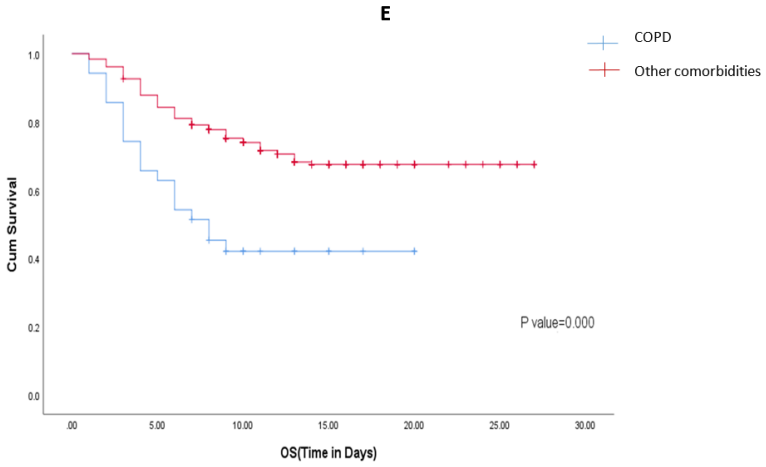

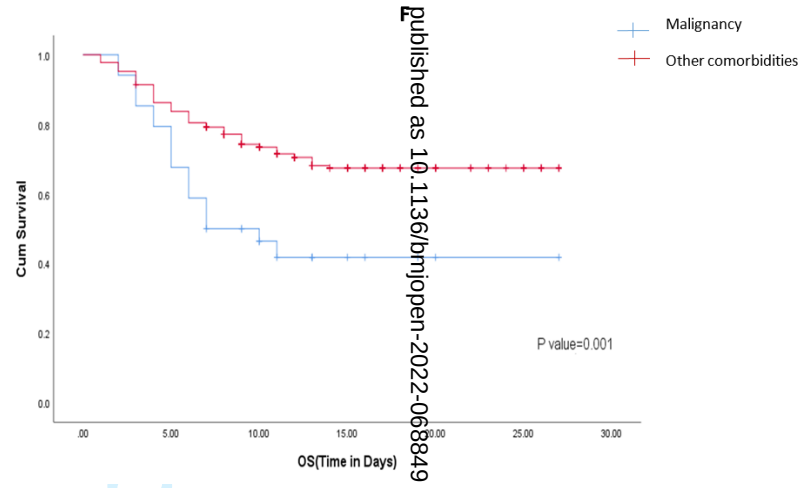

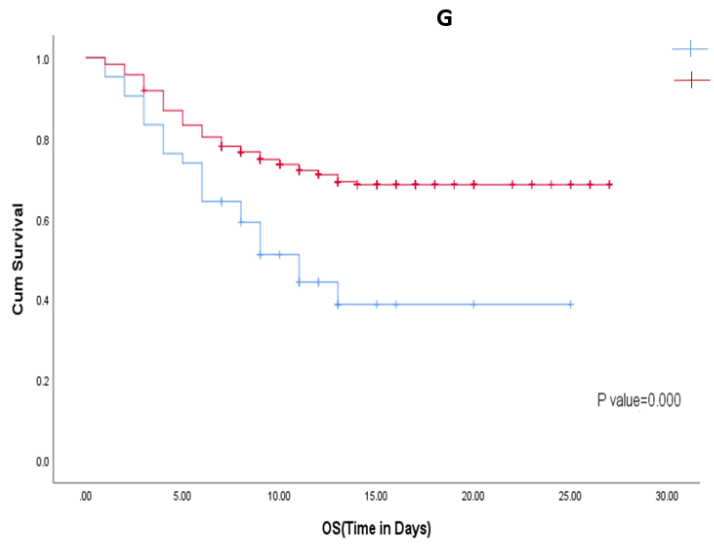

Supplementary

Table 1. Mean survival time by comorbidity group and no comorbidity group and the Log Rank test for comparison.

	Mean[a]			
			95% Confidence Interval	
Status	Estimate	Std. Error	Lower Bound	Upper Bound
comorbidity	19.691	.572	18.570	20.813
No comorbidity	27.073	.495	26.104	28.043
Overall	22.976	.470	22.055	23.896

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	38.367	1	.000

Table 2. Mean survival time by patients with ≥2 comorbidities and patients with one comorbidity and the Log Rank test for comparison.

	Mean[a]			
			95% Confidence Interval	
status	Estimate	Std. Error	Lower Bound	Upper Bound
≥2 comorbidities	17.313	.843	15.660	18.965
One comorbidity	22.482	.700	21.109	23.855
Overall	19.691	.572	18.570	20.813

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	21.297	1	.000

Table 3. Mean survival time by patients with hypertension and patients with other types of comorbidity and the Log Rank test for comparison.

	Mean[a]			
			95% Confidence Interval	
Status	Estimate	Std. Error	Lower Bound	Upper Bound
Hypertension	17.638	.777	16.115	19.160
Other comorbidities	21.549	.768	20.045	23.054
Overall	19.691	.572	18.570	20.813

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	8.339	1	.004

Table 4. Mean survival time by patients with Diabetes mellitus and patients with other types of comorbidity and the Log Rank test for comparison.

	Mean[a]			
			95% Confidence Interval	
Status	Estimate	Std. Error	Lower Bound	Upper Bound
Diabetes Mellitus	18.498	.924	16.686	20.309
Other comorbidities	20.548	.723	19.131	21.965
Overall	19.691	.572	18.570	20.813

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	3.267	1	.071

Table 5. Mean survival time by patients with COPD and patients with other types of comorbidity and the Log Rank test for comparison.

	Mean[a]			
			95% Confidence Interval	
Status	Estimate	Std. Error	Lower Bound	Upper Bound
COPD	10.975	1.347	8.335	13.614
Other comorbidities	20.350	.586	19.201	21.965
Overall	19.691	.572	18.570	20.813

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	16.849	1	.000

Table 6. Mean survival time by patients with Malignancy and patients with other types of comorbidity and the Log Rank test for comparison.

	Mean[a]			
			95% Confidence Interval	
Status	Estimate	Std. Error	Lower Bound	Upper Bound
Malignancy	14.503	1.908	10.764	18.242
Other comorbidities	20.255	.591	19.097	21.414
Overall	19.691	.572	18.570	20.813

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	11.331	1	.001

Table 7. Mean survival time by patients with Obesity and patients with other types of comorbidity and the Log Rank test for comparison.

	Mean[a]			
			95% Confidence Interval	
Status	Estimate	Std. Error	Lower Bound	Upper Bound
Obesity	13.623	1.583	10.521	16.725
Other comorbidities	20.413	.593	19.251	21.575
Overall	19.691	.572	18.570	20.813

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	12.760	1	.000

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	7-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-12

		(*b*) Report category boundaries when continuous variables were categorized	7-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.