Analysis of Risk Factors in COVID-19 Adult Mortality in Russia

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Abstract

Background and Objective: Epidemiological data obtained during the ongoing SARS-CoV-2 pandemic suggests that COVID-19 mortality has specific age and gender associations. However, limited epidemiological studies explored specific populational risk factors, including comorbidities, and patient clinical characteristics. The main aim of our retrospective cohort study was to analyze associations between age, gender, and comorbidities in deceased COVID-19 patients. **Materials and Methods:** A retrospective cohort analysis was performed to assess significant risk factors in adult patients deceased from COVID-19 infection by evaluating Electronic Medical Records and post-mortem analysis in COVID-19 patients deceased between April 2020 to October 2020. All patients underwent post-mortem evaluation along with medical history analysis, including data on disease duration, hospitalization, and clinical peculiarities. **Results:** Medical records of 1487 COVID-19 patients revealed that the prevalence of males was higher (by 23%) than females; the median age for males was 71 years of age whereas for females it was 78. The most prevalent comorbid pathologies were: hypertension, obesity, diabetes, and cancer. Males are at significantly increased risk of lethal outcome, even in younger age groups, with comorbid conditions. **Conclusion:** The study concluded that comorbidities, such as hypertension, obesity, diabetes, cancer are the most important risk factors for comorbid mortality in COVID-19 patients. In addition to lung damage, multiple organ dysfunctions may be a crucial reason for COVID-19 induced death. Special precautions, such as early hospitalization, increased monitoring, and preventative tactics should be taken for at-risk patients.

Keywords

COVID-19, comorbidity, mortality rates, SARS-COV-2

Introduction

The SARS-CoV-2 pandemic has had a devastating effect on public health all over the world. An unprecedented health crisis leading to severe acute respiratory distress syndrome (SARS) and respiratory failure has significantly burdened public healthcare systems all over the world.[1,2] According to official data from the World Health Organization (WHO), the ongoing pandemic has affected over 100 million people and caused millions of deaths worldwide as of February, 2021.[3] Official data on COVID-19 related deaths and morbidity often does not reflect the true toll of the virus, as proper reporting is complicated by increased healthcare system straining, improper data handling, and human factor.[4] In Russia, COVID-19 related deaths are thought to be 3 times more than previously reported.[5] Nonetheless, the true toll of COVID-19 within a country is measured by pathological findings. Current therapeutic modalities such as conventional therapies and vaccines have so far failed to

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curb COVID-19 spread due to extreme genomic variability of the SARS CoV-2,[2] yet massive vaccinations have brought hope to a case load decrease.

Currently, lack of effective antivirals, economic burdens, governmental denial, and improper treatment tactics have caused a rise in poor clinical outcomes.[6] Epidemiological data acquired from several countries at the beginning of the epidemic suggested that people dying from COVID-19 were generally older males with multiple comorbidities.[7,8] The majority of deceased COVID-19 patients exhibited pneumonia, acute respiratory distress syndrome, cardiac abnormality, renal complications.[9] SARS Co-V2 has been known to induce multiorgan dysfunction, which significantly burdens rehabilitation.[10-12] It is hereby crucial to accurately predict COVID-19 mortality and contributing factors that would allow clinicians to choose preventative strategies for patients with a high risk of death, despite existing political, and social setbacks.[12] The pathogenesis of acute respiratory distress syndrome associated with COVID-19 is still being studied, and emerging data reveals previously overlooked aspects in viral pathogenesis, prompting further investigation.[13] Certain factors have been shown to impact disease severity, including age, gender, and comorbid conditions.[14] The main objectives of our study were to compare data of deceased COVID-19 patient's clinical characteristics between April 2020 to October 2020, followed by the evaluation of common comorbid pathologies and blood group analysis in COVID-19 mortality in hospitals of Moscow region.

Materials and Methods

Study Design and Patients

A retrospective analysis of 1487 deceased COVID-19 patients from hospitals across Moscow regions was performed. All deceased patients were included in the study following written informed consent from near relatives or legal representatives. Analysis of patient demographic data, disease duration (including hospitalization, length of disease), aggravating conditions (comorbidities), clinical peculiarities (blood type, significant priors) was carried out. Each patient received verification of COVID-19 diagnosis prior to inclusion in the study. Patients included in the study had a confirmed COVID-19 diagnosis at time of death between April 2020 to the end of October 2020.

Electronic Medical Records (EMR)

Clinical data was extracted from the unified Electronic Medical Records (EMR) system. The EMR database was made available after acquisition of ethical approval by the Local Ethics Committee of the City Clinical Hospital No. 40, by the Moscow Region Ministry of Health. From EMR, clinical, and demographic data was extracted for further evaluation.

Pathological Evaluation

Deceased patients included in the study came from different hospitals in Moscow and had an official COVID-19 diagnosis. Postmortem diagnosis was performed according to the International Statistical Classification of Diseases and Related Health Problems: the Tenth Revision (ICD-0) codes U07.1 or U07.2. According to WHO guidelines given for COVID-19, code U07.1 confirmed the presence of the virus via laboratory testing in all deceased patients. Testing for COVID-19 was performed by real time polymerase chain reaction (RT-PCR) nasopharyngeal swab tests. Upon admission the code U07.2 was used if RT-PCR was negative or unavailable. Patients with code U07.2 underwent CT evaluation of virus-associated pneumonia and extent of pulmonary damage. All the deceased patients with a confirmed positive SARS-CoV-2 RT-PCR result, were further evaluated for pre-existing comorbidities and included in the study. Post-mortem evaluation included pathological confirmation of SARS-CoV-2 infection and full inspection of organs and tissue structures involved in the lethal outcome.[9]

Patient History Evaluation

All subjects included in the study were evaluated for possible comorbidities through review of patient medical records. Hospital records and EMR were reviewed. Patient history was evaluated and the following information was extracted for further analysis: demographic data, blood group, comorbidities, autopsy findings, medical and hospitalization history, and COVID-19 disease history. The data was collected and stored on a cloud-based resource. Individual patient's medical records were analyzed with consent from a legal representative. Comorbid conditions were identified in the cohort: if over 10% of deceased patients presented with a similar comorbid condition, it was regarded as significant. Other comorbid conditions were included in the analysis, but represented as "other" comorbid conditions.

Statistical Analysis

The significance of differences between sub-cohorts was determined using the independent *t*-test or the nonparametric Mann-Whitney *U*-test when variables were non-normally distributed. Comorbidity rates were compared using Pearson's chi-squared test or Fisher's exact test. The minimal number of cases that needed to be included in this study was calculated using power analysis. Statistical data was calculated using RStudio software, version 1.2.1335 (RStudio, Inc, Boston, MA, USA). Results are
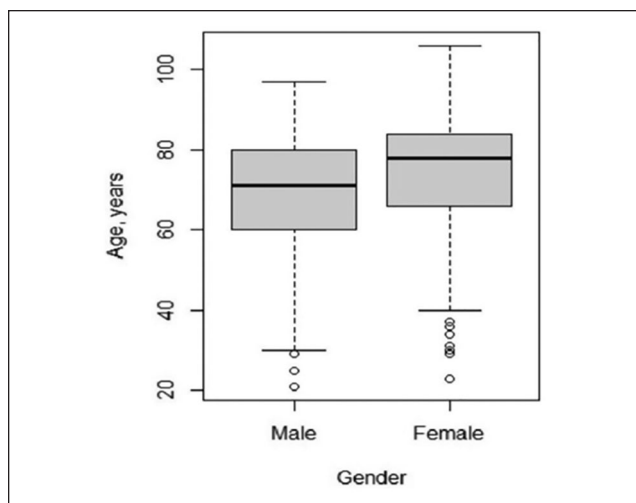
Figure 1. Frequency distribution curves pertaining to "gender, age" of deceased patients with COVID-19.

presented as means ± standard deviation or as numbers and percentages, and statistical significance was set at P-values <.05.

Results

COVID-19 Diagnosis Confirmation: Cohort Validation

Primarily, 2317 deceased patients were included in the study. Following RT-PCR and post-mortem evaluation, COVID-19 diagnosis was confirmed in 1487 patients. Patients with a negative COVID-19 RT-PCR, unconfirmed COVID-19 result were excluded from the study. As a result, 1487 deceased patients with confirmed COVID-19 diagnosis were included in the study.

Demographic Variations in COVID-19 Mortality

Age and gender distribution analysis of 1487 (844 males, 643 females) was performed. A higher COVID-19 mortality rate in males (by 23%) was observed (Figure 1 and Table 1). The median age for lethal outcome was 71 years of age among males and 78 for females.

EMR Data

The median number of days spent in the hospital for males until lethal outcome was 5, whereas for females it was 6.5. Seven percent of COVID-19 patients admitted to the hospital were deceased in less than 24 h, of which male lethal outcome was significantly more common (P < .001). No significant gender differences were noted in regard to days from symptom onset to hospitalization, time from

hospitalization to lethal outcome, time spent on artificial ventilation to lethal outcome (Table 1).

Clinical Data

The most common comorbidity in COVID-19 deceased patients was hypertension. Hypertension was prevalent in 1204 cases (81%). Importantly, hypertension was more commonly seen in deceased males (P < .001). No age association was seen for hypertension, suggesting an equally aggravating toll on overall outcome in both males and females. Obesity was the second most common comorbid condition in deceased COVID-19 patients (n = 967; 65%). Females were significantly more burdened by obesity than males (P < .001), yet deceased obese males with COVID-19 were generally younger than females (P < .05). Diabetes mellitus was present in 550 deceased patients (37%), more commonly seen in females. Cancer was a contributing factor in 178 lethal outcomes (12%). No significant gender or age related differences were noted. Other conditions, such as bronchial asthma, chronic obstructive pulmonary disease (COPD), anemia, hepatitis, gallstones, immune deficiency did not show any gender regularities. Anemia and hepatitis were associated with a lower age of lethal outcome. Unsurprisingly, immune deficiency (seen in 1 patient with acquired immune deficiency syndrome) resulted in a young age at time of death (49 years). Other comorbid conditions found in the cohort (n = 38) included lupus dermatosis, chronic tonsillitis, gastric ulcer disease, Chron's disease, endometriosis, malnutrition, etc. These conditions were not included in the final analysis, and were separated into an "Other" category, due to rare occurrence within the cohort (Table 2).

Blood Group Analysis in COVID-19 Mortality

The most prevalent blood group among deceased patients was A in 550 cases (37%), followed by group B in 476 cases (32%), group AB in 283 cases (19%), group O in 178 (12%) (Table 3). Gender association included a higher prevalence of blood group O in males, and blood group AB in females.

Discussion

Our findings have several important implications. Primarily, according to our results males tend to have a higher chance of lethal outcome, and present with a generally younger age at death. This implies the need for a widening of existing age risk groups to include younger males, especially in cases of existing comorbidities (obesity, hypertension, diabetes, anemia, hepatitis, and others). Such an action would potentially improve survival rate and outcome for currently burdened male age groups. Previously, studies have showed that the highest mortality rate is seen in elderly patients.[15,16]

Table 1. Data Extracted from Electronic Medical Records.

Criterion	Males (n = 844)	Females (n = 643)	*P*-value
Days from symptom onset to hospitalization (n ± σ)	4.30 ± 3.15	4.26 ± 2.19	.991
Time from hospitalization to lethal outcome, days (n ± σ)	5.25 ± 3.95	6.59 ± 5.36	.841
Number of diceased in under 24h after hospitalization	86	18	<.001*
Time spent on artificial ventilation, h (n ± σ)	114.63 ± 68.24	121.55 ± 42.26	.931
Age, years (mean ± standard deviation)	69.3 ± 14.1	74.4 ± 13.3	.792

*Statistically significant findings.

Table 2. Distribution of Comorbidities in Association with Patient Sex and Age.

	Males (n, % of male cohort)	Females (n, % of female cohort)	*P*-value	Male age, years (mean ± standard deviation)	Female age, years (mean ± standard deviation)	*P*-value
Hypertension (n = 1204)	713 (84.48%)	491 (76.36%)	<.001*	49.31 ± 9.26	54.32 ± 6.74	.662
Obesity (n = 967)	506 (59.95%)	461 (71.69%)	<.001*	46.40 ± 8.92	69.89 ± 6.92	.037*
Diabetes mellitus (n = 550)	283 (33.53%)	267 (41.52%)	.002*	51.35 ± 9.74	54.68 ± 12.83	.836
Cancer (n = 178)	101 (11.97%)	77 (11.98%)	.997	52.01 ± 9.78	63.22 ± 8.18	.380
Bronchial asthma (n = 20)	14 (1.66%)	6 (0.93%)	.221	66.64 ± 13.20	74.51 ± 5.92	.593
COPD (n = 21)	15 (1.78%)	6 (0.93%)	.163	64.04 ± 4.73	72.11 ± 10.30	.486
Anemia (n = 13)	4 (0.47%)	9 (1.39%)	.058	59.50 ± 9.65	68.15 ± 6.45	.473
Hepatitis (n = 6)	2 (0.24%)	4 (0.62%)	.248	58.50 ± 3.54	64.20 ± 16.77	.761
Gallstones (n = 4)	1 (0.12%)	3 (0.47%)	.197	65.00 ± 0.00	57.00 ± 10.15	.575
Immune deficiency (n = 1)	1 (0.12%)	0 (0.00%)	.383	49.00 ± 0.00	—	—
Other (n = 38)	16 (1.89%)	22 (0.34%)	.067	68.63 ± 9.55	74.10 ± 5.23	.619

*Statistically significant findings.

Table 3. Age Related Blood Group Distribution.

Blood group	Males (n = 844)	Females (n = 643)	*P*-value
O	282	268	.002*
A	254	222	.079
B	151	132	.224
AB	83	95	.005*

*Statistically significant values at $p < 0.05$.

Our findings expand on these reports by focusing on specific age-related aggravating factors in regard to gender. While showing similar data in elderly mortality rates (14.8% lethal outcome in patients over 80 years of age), our results show important tendencies in younger at-risk age groups, especially in males. For several comorbidities (hypertension, obesity, immune deficiency), the mean age at lethal outcome is under 50 years of age. This should be taken into account in further revision of existing epidemiological preventative measures and vaccination prioritization.

Our results also imply specific aggravating factors in patient assessment, which could prompt preemptive measures to be taken to high-risk individuals. Such factors include comorbid conditions (hypertension, obesity, diabetes mellitus, cancer), male gender, blood group (A, B, AB)

and age (over 65 years of age). Over 23% of local Moscow residents are older than 65 years of age and the overall mortality rate was previously reported to be under 1%,[16-18] whereas our study has shown a mortality rate of nearly 20% for senior citizens. This underlines the importance of stay-at-home orders and priority vaccinations for such patients. Such associations are generally disregarded by governmental statistics, but should be included in overall COVID-19 mortality toll.[19-21]

The found association between obesity-related lethal outcome in male COVID-19 patients is of special interest. Despite a higher mortality rate of obese females within the female cohort, obese males have a significantly younger age at death. This association can serve as a basis for investigative studies into COVID-19 mechanisms of pathological

action in obese males. Male obesity seems to be the greatest risk factor in COVID-19 mortality in the younger male population.

Blood group analysis has shown similar findings with researchers from other countries.[14,22,23] Our results show a higher lethal outcome rate in patients with A, B, and AB blood groups. In Russia, blood group associated mortality rate has important implications. In Russia, the general blood group distribution is: O (45%), A (40%), B (11%), AB (4%). In our study, the most prevalent blood group was A (37%), this distribution is similar to the typical distribution of blood groups in the broader Russian population, yet we also observed that the frequency of blood group B was higher in our sample (32%) than in the Russian population as a whole (11%). As such, individuals with blood group B may be more prone to COVID-19 lethal outcome.

The prevalent comorbidity pathologies were hypertension (81%); obesity (65%); diabetes (37%); and oncology (12%). These features are consistent with previous reports that patients with underlying comorbid conditions are more likely to develop severe disease.[24,25] Out study adds to existing data by identifying specific age and gender related peculiarities, such as a higher obese male death toll despite increased prevalence of obese females ($P < .001$), and a generally younger age at death for obese males, compared to females ($P < .05$). Our results suggest that males with aggravating conditions are generally more likely to die from COVID-19, including a higher rate of deaths within 24 h after hospitalization. The later has important clinical implications. A high death rate within the first 24 h of hospitalization suggests the need for early hospitalization of at-risk patients, despite relatively stable condition. This can help begin timely preventative measures to reduce risk of lethal outcome.

The tendencies revealed in our report imply specific pathological mechanisms behind increased lethal outcome rates in COVID-19 patients. Since literature data has shown multiorgan failure to play a significant role in increased lethal outcome,[26,27] we can further hypothesize that specific comorbid conditions, age, and gender peculiarities play a direct role in disease severity. Based on our findings, obese males with hypertension may have a greater risk of uncontrollable viral spread and therefore multiorgan pathology. While regularly, normal immune defense mechanisms mediate a recovery, in patients with aggravating factors, a cytokine storm response can lead to an uncontrollable pathologic reaction. Indeed, the comorbid conditions identified in our study have shown to play a direct role in causing acute complications of respiratory diseases, inducing a cytokine storm.[28,29] Therefore, the cytokine storm is another important factor contributing to COVID-19 lethality and is enhanced by antibody-dependent enhancement in patients with liver, vascular, cardiac, and kidney dysfunctions.

Cardiac morbidity induced by COVID-19 is more severe in patients with existing comorbidities.[30,31] This finding can explain increased lethal outcome in both genders with such conditions as hypertension and obesity. Other risk factors of cardiac complications include advanced age, male gender, and A, B blood groups. This observation is consistent with our findings. The severity of COVID-19 is generally reported to be higher in patients with pre-existing comorbid cardiovascular conditions.[31-34] This is due to viral-associated increased coagulation activity due to marked rise in d-dimer concentrations.[35] As such, obese patients, and those with hypertension and diabetes mellitus are at increased risk of COVID-19 lethality. Ischemia and thrombosis have been known to cause lethal outcome in such patients.[36,37] Furthermore, ACE-2 (angiotensin converting enzyme 2) is reported to be expressed on the vascular endothelial cells and myocytes, which may further enhance SARS-CoV-2 induced vascular-related pathophysiology in deceased patients.[2] ACE receptors have been shown to be more concentrated in males,[38] which may account to increased overall lethality of the male population, especially with comorbid conditions, as seen in our results.

The limitations of our study include cohort related limitation, as our study focused mainly on hospitalized patients, while patients who died at home or in care homes were not included.[39] However, the study is significantly informative as medical records of deceased COVID-19 patients were reviewed to compare clinical characteristics and disease progression in patients with comorbidities among the subset of hospitalized patients. Our study evaluated age and gender associations with comorbidities in deceased COVID-19 patients in the most central region of Russia. The revealed tendencies can be considered to be more severe in other regions of Russia due to economic and local healthcare burdens.

Conclusions

Our findings suggest that age, gender, and underlying comorbid diseases including, hypertension, obesity, diabetes, cancer are the most important risk factors for COVID-19 related morality. COVID-19 infection plays an important role in the death of patients due to onset of multiple organ dysfunctions, a condition exacerbated by existing pathology of the cardiovascular system. Thus, our results may benefit medical professionals in epicenters of COVID-19 outbreak to confront rapid surges in confirmed cases, which may overwhelm healthcare centers. Importantly, our results show a generally increased risk of lethal outcome in males, with a notable age-related burden: younger males tend to die more often in presence of comorbidities. As such, special attention should be given to patients with aggravating comorbidities, which may be suggested to be placed under observation with symptoms onset. It may be beneficial to

revise existing risk stratification strategies to include younger patients with aggravating comorbid conditions. Preventative measures should be taken to improve overall survival of at-risk groups identified in our study.

Abbreviations

- COVID-19: Coronavirus infection 2019
- SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2
- WHO: World Health Organization
- RT-PCR: Real time polymerase chain reaction

Author Contributions

YK, ST, AA, VN contributed to conception and organization of the research project, drafted the main manuscript text. LG and AA were involved in study conception, participated in design and coordination, and helped to draft the manuscript. YK, ST, VN performed the experiments and acquired the data. VN, MY was responsible for data acquisition. LG, ST MY: writing, review and editing; YK, LG, VN: analysis and interpretation of data, wrote manuscript, and approved the final version of the manuscript. All authors have read and agreed to the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Institutional Review Board Statement

The study was reviewed and approved by the Ethics Committee of the City Clinical Hospital No. 40, Moscow, Russia (within the department of Pathology).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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Data Availability Statement

All relevant raw data are freely available to any researchers who wish to use them for non-commercial purposes while preserving any necessary confidentiality and anonymity. The datasets are available on request to the corresponding author.

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