Risk Factors Associated With COVID-19 Mortality Among Patients Hospitalized in Yerevan, Armenia: A Research Grant Proposal

Master of Public Health Integrating Experience Project

Research Grant Proposal Framework

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List of abbreviations

ACE-2 - angiotensin-converting enzyme-2

ARDS - acute respiratory distress syndrome

AUA - American University of Armenia

CDC - Centers for Disease Control and Prevention

COPD - chronic obstructive pulmonary disease

COVID-19 - coronavirus disease 2019

CRP - C reactive protein

CT - computer tomography

DNA - desoxyribonucleic acid

ICU - intensive care unit

IRB - institutional review board

MERS - middle east respiratory syndrome

MoH - Ministry of Health

mRNA - micro ribonucleic acid

NCDC - National Center for Disease Control

NAAT - nucleic acid amplification test

PCR - polymerase chain reaction

RDT - rapid diagnostic test

SARS - severe acute respiratory syndrome

SARS-Cov-2 - severe acute respiratory syndrome coronavirus-2

VOC - variant of concern

VOI - variant of interest

WHO - World Health Organization

US - United States

UK - United Kingdom

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Executive Summary

A new kind of coronavirus was first identified in Wuhan, Hubei province, China in 2019. Due to structural similarities to the virus that caused severe acute respiratory syndrome, it was named SARS-CoV-2, and the illness caused by that virus was named COVID-19. The virus spread from its origins, resulting in a pandemic that has impacted every country in the world. As was a trend for many countries worldwide, Armenia also experienced multiple waves of infection resulting in not only cases but also deaths. The most extensive number of deaths were observed during the predominance period of the Delta variant in Armenia, which was one of the variants of concern reported by World Health Organization, due to its associated increase in disease severity and mortality due to COVID-19. Many studies have examined risk factors associated with death due to COVID-19 worldwide, but none have specifically looked at Armenia. Therefore, this study aims to explore the independent medical, laboratory, clinical, behavioral, and demographic characteristics associated with COVID-19 mortality in Armenia from July 1, 2021, to December 31, 2021. A retrospective cohort study with an estimated sample size of 2,076 patients will be utilized to answer this research question. Inclusion criteria are being patients aged 18 and above and tested positive via SARS-CoV-2 and hospitalized in the Saint Grigor Lusavorich or Nork Infectious Disease hospitals for at least 48 hours. Patients who were transferred to another hospital will be excluded from the study. Cox proportional hazards models will be utilized to identify potential risk factors associated with death due to COVID-19. An estimated 5 months and 3,050,000 drams will be needed to complete the study. Findings from the study will be presented to policymakers and health care professional with the hopes of developing targeted strategies to reduce COVID-19 mortality in Armenia.

1. Introduction

1.1 Background information

Coronaviruses are a broad group of viruses that can induce a large spectrum of respiratory illnesses among people and have led to a number of outbreaks and epidemics worldwide.[1,2] In 2002, a novel coronavirus was identified in southern China that caused severe acute respiratory syndrome (SARS). Ten years later, in 2012, another epidemic was due to a distinct coronavirus first reported in Saudi Arabia which caused a different disease named middle east respiratory syndrome (MERS).[2] Most recently, in December 2019, a respiratory illness outbreak was reported in Wuhan Hubei Province, China, which was called coronavirus disease 2019 (COVID-19).[3] This disease was caused by a new kind of coronavirus which had structural similarities with the virus that caused SARS. Hence, the novel virus was named SARS-CoV-2.[4] Because of the wide spread of the virus, on the 11th of March 2020, the World Health Organization (WHO) announced COVID-19 a pandemic.[4] According to the WHO, as of May 23, 2022, 525,778,539 confirmed cases of COVID-19 and 6,277,818 deaths were reported, and a total of 11,445,077,393 vaccine doses were administered worldwide.[5]

SARS-CoV-2, similar to other respiratory infectious diseases, is spread by infected individuals when coughing, sneezing, speaking, singing, or breathing. An individual can become infected through short-range and long-range airborne transmission, droplet transmission, as well as when touching eyes, nose and mouth after contact with surfaces and objects that the virus has contaminated.[6] People that are infected with SARS-CoV-2 but do not have any symptoms and cases who are in the prodromal stage of the disease are also found to spread the virus.[7]

COVID-19 symptoms have been reported to range widely, and the disease severity ranges from mild to critical, and in some cases even to death.[8] SARS-CoV-2 cohere to angiotensin-converting enzyme-2 (ACE-2) receptors on the surfaces of the cells of the lung tissue and respiratory tract, damaging the cells and resulting in the common respiratory symptoms that are generally observed.[9] Mild to moderate stages include mild pneumonia and symptoms including fever, dry cough, tiredness, myalgia, and loss of smell or taste.[10,11] Gastrointestinal symptoms such as diarrhea and vomiting might also be present.[12] Neurologic symptoms have also been identified during these stages, including dizziness, headache, taste and smell dysfunction, and weakened consciousness.[13] Due to the nature of the virus, in the more severe stages, viral pneumonia, dyspnea, and consequently low oxygen saturation can occur among COVID-19 patients.[11,14] The critical stage includes respiratory failure (acute respiratory distress syndrome(ARDS)) and multisystem dysfunction.[8]

1.2 COVID-19 related mortality

According to the WHO, a probable COVID-19 case is "a patient who meets clinical criteria and is a contact of a probable or confirmed case, or linked to a COVID-19 cluster; a suspect case with chest imaging showing findings suggestive of COVID-19 disease; a person with recent onset of loss of smell or loss of taste in the absence of any other identified cause" and a confirmed case is "a person with a positive nucleic acid amplification test (NAAT); a person with a positive SARS-CoV-2 antigen-rapid diagnostic test (RDT) and meeting either the probable case definition or suspect criteria; an asymptomatic person with a positive SARS-CoV-2 Antigen-RDT who is a contact of a probable or confirmed case". A death due to COVID-19 is "a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19

case, unless there is a clear alternative cause of death and should be counted independently of preexisting conditions" per the WHO definition.[15]

The general influence of the COVID-19 pandemic has been much greater than the deaths from COVID-19 alone.[16] Estimation of excess deaths can give valuable details about the possible load of mortality associated with the COVID-19 pandemic, accounting for deaths linked to COVID-19.[17] According to WHO excess deaths are interpreted as "the difference between the observed numbers of deaths in specific time periods and expected numbers of deaths in the same time periods". A systematic analysis of COVID-19 related deaths revealed that although the reported overall deaths from COVID-19 between January 1, 2020, and December 31, 2021, were 5,940,000, the estimated COVID-19 related mortality, calculated by excess morality, was 18,200,000. These differences were mainly due to the overburdened condition of healthcare systems which led to the neglect of other healthcare issues.[16]

1.3 SARS-CoV-2 mutations and preventive measures

Many preventive measures were implemented worldwide to restrain the spread of SARS-CoV-2, including lockdowns, masks, restrictions on social interactions, and vaccines.[14] Development of the vaccines, fortunately, took less than 12 months, becoming a significant accomplishment, as the vaccine development process usually takes years.[18,19] Many COVID-19 vaccines have been developed based on the four biological types of vaccines: nucleic acid (mRNA or DNA), viral vector, protein subunit, and inactivated virus.[20] Vaccination has been shown and remains a highly effective way of preventing COVID-19 severity and mortality.[19] As a result of viral replication, mutations occur naturally.[21,22] Most of them do not change the viral

properties, but some of them can change the behavior of the viruses and lead to increased transmission or compromise the effectiveness of the developed vaccines.[22–24] Monitoring SARS-Cov-2 dynamics is crucial for future improvement and production of new mutation-resistant vaccines.[23] For that reason, countries have been tracking variants and the WHO established a system of categorization of these subtypes of SARS-CoV-2. Variants of interest (VOIs) and variants of concern (VOCs) are considered to pose an increased risk for public health globally. VOIs are variants with specific mutations that can potentially lead to changes in transmissibility, disease severity and treatment, as well as vaccine efficacy.[22] In addition to the characteristics of VOIs, VOCs have significantly higher transmissibility and are associated with increased disease severity and mortality. They may also significantly diminish treatment and vaccine efficacy.[22] A noteworthy example is the VOC named Delta, which was first identified in India at the end of 2020. It was more transmissible and was associated with increased disease severity and mortality worldwide compared to the previous subtypes.[25] Another VOC was identified at the beginning of 2022, which was named Omicron. Omicron had a higher tropism for the upper respiratory tract yet caused mild symptoms when compared to other variants of SARS-CoV-2. However, the transmissibility was significantly higher than in other variants.[26] These VOCs are important to note for their increased transmissibility and thus potential for greater impact on the morbidity and mortality due to COVID-19 in the population.

Factors such as weak preventive measures and poor vaccination coverage of the population may allow more transmissible variants to arise and disseminate.[24] Essential factors for achieving global immunity worldwide are the affordability of vaccines in low- and middle-income countries and poorer and marginalized populations of high-income countries.[27,28]

Otherwise, the pandemic can continue, as new mutations can occur and exacerbate the situation.[28]

1.4 Situation in Armenia

As of January 1, 2021, the population of Armenia was estimated at 2,963,300. Males were 47.2% of the total population. At the beginning of 2021, the urban population was 64% of the total population. As of January 1, 2021, the age distribution of Armenian population was as follows: 21.4% ages 0-15, 63.5% ages 16-62, 15.1% ages 63 and above. Life expectancy at birth for the total population, males and females were 73.5, 68.4 and 78.6 respectively.[29]

The first case of COVID-19 in Armenia was reported on March 2, 2020.[30] The government declared a state of emergency and a national lockdown on March 16, 2020.[31] The state of emergency was lifted on May 14, 2020.[32] The first death due to COVID-19 was reported on March 26.[33] As was the trend globally, Armenia experienced multiple waves. The morbidity and mortality from COVID-19 increased significantly over the first several months, but Armenia managed to flatten the curve by the end of summer 2020.[34] Unfortunately, that was short-lived, as war broke out in Artsakh, leading to increased COVID-19 morbidity and mortality.[35] Due to the cyclical nature of the pandemic, the number of deaths and confirmed cases dropped again by the end of 2020.[35] On the 2nd of August, 2021, the National Center for Disease Control (NCDC) of Armenia reported that the Delta subtype of SARS-Cov-2 was identified in specimens of positive tested people.[36] As a result, the number of confirmed cases and deaths grew sharply at the same time the Delta variant started to rapidly disseminate around the country as it was found to be associated with increased disease severity and mortality.[25] The mortality due to COVID-19 increased approximately fourfold at the end of October compared

with August 2021. Eventually, as with all of the waves, the number of cases and deaths dropped at the end of December 2021.[34] For the period from January 2021 to September 2021 the number of reported deaths due to COVID-19 was 2.8 times higher, when compared to the same period of 2020, which partially corresponds to the predominance period of Delta variant in Armenia.[29] A large scale systematic review revealed that the excess mortality for Armenia was estimated to be 20,600 between January 1, 2020, and December 31, 2021.[16] However the reported COVID-19 deaths were 7,975 for the same time period.[29]

On the 8th of January 2022, Omicron was identified in specimens of positive tested people.[37] After the Omicron variant's presentation in the county, the number of confirmed cases and deaths started to grow until the peak in the middle of February.[34]

As of 2020, the highest mortality rates due to COVID-19 were observed in Yerevan, Kotayk, and Lori marzes with the lowest mortality rate recorded in Syunik marz. In all marzes and Yerevan, COVID-19 mortality rates were higher among males than among females. The picture among the population under 65 years was similar and the mortality rates among males and females were 70.4 and 48.2 per 100,000 population, respectively. COVID-19 mortality rates increase with increasing age, and the highest mortality rates were observed among 60-69 and above 70 age groups in Armenia in 2020.[29] According to the NCDC, of the 3,089,295 total tests administered, have been 422,939 confirmed cases, with 8,624 deaths, 412,221 recoveries, and 388 patients receiving treatment as of May 23, 2022.[38]

Vaccines were made available for the population from April 2, 2021, and people could freely receive any vaccine type they preferred. From their first availability, the Ministry of Health

(MoH) and public health professionals have embarked on large public awareness campaigns about the importance of vaccination and its crucial role in prevention of a severe course of disease and mortality.[39] As of May 22, 2022 the Ministry of Health of Armenia reported that 2,193,307 doses of COVID-19 vaccine were administered, of which first, second dose and boosters were 1,132,945, 1,003,530, and 52,757, respectively.[40]

As of May 9, 2022, among the total female population eligible for vaccination in Armenia, 42.7%, 37.6% and 1.9% had their first, second and booster doses of the vaccine, respectively. As for the eligible male population, 57.9%, 52.4% and 2.5% had received their first, second and booster doses, respectively. Vaccination status varied by age as well. For those 18-34 years, 46.5%, 39.7% and 1.7% received their first, second and booster doses, respectively. Among the population aged 35-64, 53.4%, 48.5% and 2.4% had received their first, second and booster doses, respectively. And finally, among the population aged 65 and above, 42.9%, 39.3% and 2.8% had received their first, second and booster doses, respectively.[40]

1.5 Risk factors for COVID-19 mortality

COVID-19 mortality has been found to be associated with age, gender, ethnicity, socioeconomic status, outdoor environment, smoking status, clinical and laboratory characteristics, and also with having many comorbidities such as hypertension, diabetes mellitus, obesity, heart failure, different type of dementias, pulmonary diseases, cancer, renal and liver diseases.[41–44]

1.5.1 Demographic characteristics

Sex assigned at birth has been shown to be associated with death due to COVID-19. According to several studies conducted in different countries, COVID-19 mortality was significantly associated with the male sex.[45–47] The COVID-19 mortality rate was lower among

women than men, which could be explained by genetic factors and hormones.[48] Other studies linked the difference to greater appearance of the ACE-2 receptors among males.[49] A large cohort study conducted in New York City reported that older age and male sex were associated with an increased risk of COVID-19 mortality.[50] A meta-analysis of 59 studies reported that male sex was an independent risk factor associated with increased COVID-19 severity and mortality.[45–47,51] Many other studies also confirm that male sex is associated with a higher risk of mortality.[52–54]

Multiple studies conducted in different countries have reported that mortality from COVID-19 was associated with age.[45,52,55,56] A study conducted in Iran revealed that a one-unit increase in age increased the odds of COVID-19 mortality by 3%.[57] A large-scale population-based study in the United States (US) revealed that COVID-19 deaths are more frequent with increasing age, and the most substantial independent risk factor for mortality was age 65 and above, which had 11 times the risk of death form COVID-19 when compared to the patients aged 19-45.[58]

Race and ethnicity have also been shown to be associated with COVID-19 mortality. A medical record-based study conducted in the US revealed that being African-American was associated with higher odds of COVID-19 mortality.[59] According to the Office for National Statistics of England, from January 10, 2022 to February 16, 2022 mortality rates due to COVID-19 were greater for quite a few ethnic minorities, and especially for the Bangladeshi and Pakistani groups when compared with the White British group.[60] Other studies also note that ethnic minorities and African-American people are at higher risk of COVID-19 mortality.[61–63] These differences could be attributed to ethnic and racial health care disparities due to discrimination and preliminary health condition of marginalized goups.[64,65]

1.5.2 Clinical and laboratory characteristics

Several clinical and laboratory characteristics have been shown to be significantly associated with an increased risk of death due to COVID-19.[66,67] High systolic blood pressure and tachypnea are among clinical characteristics that were found to be associated with higher odds of COVID-19 mortality.[50,68] A study conducted in China revealed that high oxygen saturation was associated with decreased risk of mortality due to COVID-19 after adjusting for age and sex.[69,70]

Low estimated glomerular filtration rate, increased interleukin-6, D-dimer, C reactive protein (CRP), creatinine, glucose, white blood cell count (WBC), platelet count, and troponin levels were among the laboratory characteristics found to be associated with increased odds of COVID-19 mortality.[50,68,70,71]

1.5.3 Comorbidities

Quite a few studies from different countries claim that many comorbidities are associated with an increased risk of COVID-19 mortality. Several studies reported that the risk of mortality due to COVID-19 was significantly higher among people with chronic obstructive pulmonary disease (COPD).[72,73,74] In another study, interstitial lung disease and lung cancer were significant risk factors for COVID-19 mortality.[74] Moreover, heart failure, coronary heart disease, and cardiomyopathies have been found to be significant predictors for COVID-19 mortality.[75,59]

It has been previously established that people who have diabetes are more susceptible to any infectious disease, including COVID-19, than the general population.[76–80] Several studies revealed that the risk of mortality due to COVID-19 was 2-3 times higher among type II diabetic patients when compared to non-diabetic patients.[77–80] According to several studies, the risk of COVID-19 mortality was higher among patients with hypertension when compared to non-hypertensive patients.[81,82] Many studies also indicated that liver disease and obesity were

associated with increased risk of COVID-19 mortality.[59,72] Presence of a renal disease was associated with increased risk of mortality due to COVID-19, according to another study.[85]

Cancer, especially different types of blood cancer, increase the risk of death from COVID-19, according to various studies.[59,83,84] Breast and prostate cancer were found to be associated with an increased risk of death from COVID-19 among patients aged 45-65.[59,74]

1.5.4 Smoking status

Smoking status has also been shown to be associated with COVID-19 mortality. Smoking may impair lung function and immune defense of the respiratory tract, which can result in higher susceptibility to respiratory infections, including COVID-19, among smokers.[86,87] According to a recent meta-analysis, current smokers have a greater risk of mortality from COVID-19 than former and never smokers.[87]

1.5.5 Vaccination status

COVID-19 vaccines have been detected to be considerably effective in preventing disease severity and mortality.[88] The US Centers for Disease Control and Prevention (CDC) reported that from October to November 2021, the risk for COVID-19 mortality among unvaccinated people was 53.2 times the risk of fully vaccinated people who had a booster dose and 12.7 times the risk of fully vaccinated people who did not attain a booster dose.[89] It is important to mention that among the population above 50 years old, the booster dose had the highest effect on preventing infection and death compared with fully vaccinated people of the same age. During the predominance period of the Delta variant, weekly average age-standardized death rates in the US were higher among unvaccinated people (1.5-11.4 per 100,000 population) when compared to fully vaccinated people (0.1-0.7 per 100,000 population).[89] In England, the risk for COVID-

19 associated death was 81.2% lower among the people who attained the second dose at least 21 days ago when compared to unvaccinated people, from July to December 2021.[90]

1.6 Study rationale and specific aims

COVID-19 has become a big challenge worldwide and poses a massive problem for Armenia's health care system as well. Mortality due to COVID-19 increased significantly, especially during the dissemination period of the Delta variant and due to low vaccination coverage. Hence, this study aims to explore predisposing factors for COVID-19 mortality in Armenia, which will help to improve the management and care of COVID-19 patients. Furthermore, vulnerable populations with a higher risk of developing severe outcomes from COVID-19 could be identified with the help of this study, which could be a base for developing future prevention strategies.

Thus, the research question for the proposed study is: What are the independent demographic, behavioral, medical, clinical, and laboratory risk factors associated with COVID-19 mortality in Armenia?

2. Methods

2.1 Study design and settings

A medical record-based multi-center retrospective cohort study will be conducted to explore the risk factors associated with COVID-19 mortality. This study design was chosen due to the nature of the data collected as well as the fact that it is not costly and time-consuming.
The study will include two major hospitals treating COVID-19 patients from July 1, 2021, to December 31, 2021: Nork Infectious Disease and Saint Grigor Lusavorich hospitals. These two hospitals have been treating only COVID-19 patients from the beginning of the pandemic. Patients were transferred to these hospitals only if they tested positive via SARS-CoV-2

polymerase chain reaction (PCR) test in the polyclinic or the hospital they initially presented to. Thus, these hospitals had the most extensive number of hospitalized COVID-19 patients.

2.2 Eligible population

The target population is all patients aged 18 and above who tested positive via the SARS-CoV-2 PCR test within 14 days before admission and were admitted to Nork Infectious Disease or Saint Grigor Lusavorich hospitals from July 1, 2021, to December 31, 2021. According to the definition of CDC and practice in Armenia, the positive PCR tests for SARS-CoV-2 are valid for 14 days, after which the patient had to test again before transfer or admittance to these hospitals.[7] Another inclusion criterion will be at least 48 hours of hospitalization. Inclusion of patients who were hospitalized for at least 48 hours will increase the possibility of complete information. Patients transferred to other hospitals will not be included in the study, as information about the outcome of the patient will not be able to be obtained.

2.3 Study variables

The dependent outcome variable is death due to COVID-19 according to the definition of WHO.[15] Independent variables are possible risk factors for COVID-19 mortality. Demographic characteristics that will be included in the study are age, sex, and place of residence. As for comorbidities diabetes mellitus, heart disease, cancer, pulmonary disease, liver disease, and kidney disease will be included. Oxygen saturation, and blood pressure are among the clinical characteristics that are chosen in the scope of this study. The presence of pneumonia will be recorded based on tomography (CT) scan confirmation. Finally, laboratory characteristics that will be included in the proposed study are WBC count, platelet count, and CRP. The thresholds for the laboratory and clinical risk factors are presented in Table 1.[91–95]

Vaccination and current smoking status will be collected from the inpatient medical records. Hospital where the patient was hospitalized will be another variable. This variable will help to compare the performance of these two hospitals.

The data will be extracted from the medical histories of study participants. The first measurement will be taken for the continuous clinical and laboratory variables, as afterward, they could change due to treatment.[96] The variables were chosen regarding the availability of data in patients' medical histories and the literature review (Table 2).

2.4 Sample size calculation and sampling

The following sample size calculation formula for comparing two group proportions was used:

$$n = \frac{\{z_{1-\alpha/2}\sqrt{2\bar{p}(1-\bar{p})} + z_{1-\beta}\sqrt{(P_1(1-P_1) + P_2(1-P_2)}\}^2}{(P_1 - P_2)^2}$$

The estimated proportion of deceased patients in the “exposed” group is represented by P_1 and P_2 in the “unexposed” group. *P-bar* is the mean of P_1 and P_2, and *n* is the sample size for each group. The predefined level of significance is 5% and the desired power is 80%. Potential sample sizes were calculated based on estimates for P1 and P2 from all proposed risk factors. The calculation based on sex resulted in the largest sample size, and thus was chosen to ensure that the study will be able to detect significant differences between "exposed" and "unexposed" patients for all proposed risk factors.

According to a large-scale, medical record-based study with more than 120,000 observations, the mortality due to COVID-19 was found to be 14% and 10% for men and women, respectively.[97] Therefore:

$\bar{p}$= (0.14+0.10)/2=0.12

$$n = \frac{\{1.96\sqrt{2 * 0.12 * (1 - 0.12)} + 0.842\sqrt{0.14 * 0.86 + 0.10 * 0.90}\}^2}{(0.14 - 0.10)^2}$$

n=1038, in each group

Hence, the total sample size will be 2,076.

Systematic random sampling will be used to obtain the study sample. Two hospital ID lists will be merged and shuffled with the help of software. The total number of COVID-19 hospitalized patients during the defined period will be divided by 2,076 to obtain a sampling interval (n). Afterward, a number will be picked out of that range with the help of a random number generator as a starting point. Every n^{th} patient from the admission list of the hospitals will be included.

2.5 Data management and analysis

Before the actual data collection in the field, two data collectors will be trained to understand the principles of data extraction and become familiar with the study protocol. As a pre-test, they will extract the data from the medical records of five patients, which will not be included in actual fieldwork. The interobserver agreement will be calculated with the help of the Kappa coefficient.

The research coordinator will visit the hospitals, get the admission lists and export the record ID numbers to an excel file. From these files the study participants will be sampled. Self-generated ID numbers will be given to each record in a separate excel file. Data collectors will then go to the archives and collect the variables on paper standardized data collection forms (Appendix 1). The data collection form was self-developed, based on the literature review.[98] Afterward, all variables will be entered in an excel file and exported to the statistical software. Double data entry will be conducted, and the two datasets of the collected data will be merged to ensure that the collected data does not have any technical mistakes.

STATA software (13.0) will be used for data management and analysis, which will be done by the data analyst. Exploratory analysis will be conducted to get familiar with the data for further analysis. This will include data visualization with the help of box plots, as well as histograms to understand the type of distribution for continuous variables. A check for missing data will also be done. Variables with more than 50% percent missing values will not be included in the inferential analysis stage.

Descriptive analysis will be conducted, and the characteristics of the study population and the risk factors among the study population will be presented (proportions, means, and interquartile ranges).

The Cox proportional hazards model will be used to identify risk factors associated with mortality due to COVID-19. This method was chosen since it is often used to investigate the association between several risk factors and the patient's survival, while also taking into consideration the time when the event of interest happened. Hence both the event and timing are significant in this analysis technique. Additionally, this model assumes that the effect of the risk factor on the outcome is continually consistent over time. Second assumption of this regression model is non-linearity. Third assumption is that there are no temporal changes in the effect of risk factor on outcome.[99]

Bivariate analyses of each risk factor and the outcome will first be conducted, and hazard ratios, 95% confidence intervals, and p-values will be calculated for every each. All risk factors with a significant hazard ratio, defined as having an associated p-value <0.05, will be included in the multivariable analysis. Hazard ratios, 95% confidence intervals, and p-values will be presented as the result of the multivariable analysis. The proportional hazards assumption will

be tested by examining the Schoenfeld residuals. Martingale residual will be used for checking non-linearity assumption.

3. Logistic considerations and timeline

Approval from the administrations of Nork Infectious Hospital and Saint Grigor Lusavorich Hospital is needed to obtain information on COVID-19 patients' admission lists and inpatient medical records. This approval will also be needed before understanding the number of COVID-19 patients each had during the study period. To ensure the feasibility of this study, confidence that sample size will be met is necessary. Although there is no publicly available data on the number of COVID-19 hospitalization by hospital, there is information on overall deaths and hospitalizations in Armenia. During the proposed study period, there were 3,458 deaths and 119,759 confirmed cases of COVID-19 in Armenia.[100] Additionally, there is no information on the distribution of deaths and hospitalizations by marz during the study time period, but in 2020 according to National Institute of Health of Armenia, 48.4% of the total COVID-19 deaths in Armenia were reported in Yerevan. Therefore, there is considerable confidence that the necessary sample size will be achieved.

Five months will be needed to carry out the study. Three months will be allocated to training, pre-test, and data collection from the hospital's inpatient medical records. Afterward, two months will be used for data analysis and report preparation (Table 3). The results of the study and derived future recommendations will be presented to the hospitals that were included in the study for the medical and administrative staff. This study findings will help to identify the vulnerable populations and improve the management of care especially among them.

4. Ethical considerations

This study protocols comply with the requirements of the American University of Armenia (AUA) Institutional Review Board (IRB) requirements. Medical record ID numbers will be obtained from the admission lists of study hospitals. Afterward, self-generated ID numbers will be given to each patient to ensure confidentiality, and the list linking hospital and study ID numbers will be destroyed after the end of this study. The data will be kept in a password-protected file. The data will be available only to the research team. Databases will be preserved on encrypted computers.

5. Budget

The estimated budget for conducting this study includes administrative and personnel expenses. A data coordinator will be needed for study planning and management. Two data collectors will be needed, as the double data entry is planned. A research analyst will be needed for the data analysis portion of the study. The research coordinator, data collectors, and statistician will receive a monthly salary. Operational costs will include office renting and utility payments. The estimated budget is 3,050,000 Armenian dram (AMD). See more details in Table 4.

6. Future implications

The proposed study will be the first one examining risk factors associated with COVID-19 mortality in Armenia. The findings of the study will be presented to the attention of decision-makers, health care professionals and public health professionals. As there is a research gap regarding the risk factors associated with COVID-19 in Armenia, this study can serve as a basis for policymakers to develop future prevention strategies which can be especially effective for vulnerable populations. Moreover, after the implementation of the proposed study, it would be

beneficial to conduct a large-scale population-based investigation to understand the prevalence of risk factors associated with COVID-19 mortality for the general Armenian population.

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Tables

Table 1. Thresholds for the selected risk factors

Risk factor	***Threshold***
Elevated CRP	>40 mg/L
Elevated WBC	$11*10^9$/L
High blood pressure	≥140/90
High platelet count	$450*10^9$/L
Low oxygen saturation	<90%

Table 2. Study variables

Variable	***Type***	***Options***
Death due to COVID-19	Binary	Yes No
Age	Continuous	
Sex	Binary	Male Female
Place of residence	Categorical	Yerevan Other Marzes
Diabetes mellitus	Binary	Yes No
Heart disease	Binary	Yes

		No
Cancer	Binary	Yes No
Pulmonary diseases	Binary	Yes No
Liver disease	Binary	Yes No
Kidney disease	Binary	Yes No
Oxygen saturation (%)	Continuous	
Blood pressure (mmHg)	Continuous	
Pneumonia	Binary	Yes (CT scan) No
White blood cell count (cell/L)	Continuous	
Platelet count (cell/L)	Continuous	
C reactive protein (CRP) (mg/dl)	Continuous	
Vaccination status	Binary	Yes No
Smoking status (current)	Binary	Yes No

*Categories if the data is available

Table 3. Timeline

Activity	M1*	M2	M3	M4	M5
IRB approval, approval from hospitals	X				
Pre-test data collection	X				
Data collection	X	X	X	X	
Data management	X	X	X	X	X
Data analysis and interpretation				X	X

*Month

Table 4. Estimated Budget

*Armenian dram

Budget item	**Appointment type**	**Number of required units**	**Amount**	**Total**
Data collector 1	monthly	3	150,000 AMD*	450,000 AMD
Data collector 2	Monthly	3	150,000 AMD	450,000 AMD
Research coordinator	monthly	6	200,000 AMD	1,200,000 AMD
Statistician	monthly	1,5	200,000 AMD	300,000 AMD
Office rent	monthly	6	100,000 AMD	600,000 AMD
Stationery supplies, paper printing	-	1	20,000 AMD	20,000 AMD
Other costs	-	1	30,000 AMD	30,000 AMD
Total				3,050,000 AMD

Appendices

Appendix 1.

Risk Factors Associated With COVID-19 Mortality Among Hospitalized Patients in Yerevan, Armenia: A Research Grant Proposal **Data Collection Form**		
Data collector ID _____ **Date__/__/___(dd/mm/yyyy)**		
1.	***Self-generated ID number***	_____
2.	***Death due to COVID-19***	1. Yes
		2. No
3.	***Demographic characteristics***	
	a. Age (years)	_____
	b. Sex	1. Male
		2. Female
	c. Place of residence	1. Yerevan 2. Lori 3. Ararat 4. Armavir 5. Aragatsotn 6. Gegharkunik

		7. Kotayk 8. Shirak 9. Syunik 10. Vayots Dzor 11. Tavush
4.	***Comorbidities***	
	a. Diabetes mellitus	1. Yes
		2. No
	b. Heart disease	1. Yes
		2. No
	c. Cancer	1. Yes
		2. No
	d. Pulmonary disease	1. Yes
		2. No
	e. Liver disease	1. Yes
		2. No
	f. Kidney disease	1. Yes
		2. No
5.	***Clinical characteristics***	
	a. Oxygen saturation (%)	_____
	a. Blood pressure (upper/lower,	____/____

	mmHg)		
	b. Pneumonia	1. Yes (If CT scan confirmation is present)	
		2. No	
6.	***Laboratory characteristics (first measurements)***		
	a. White blood cell count (cell/L)	_____	
	b. Platelet count (cell/L)	_____	
	c. C reactive protein (CRP) (mg/dl)	_____	
7.	***Vaccination status**** *If available	1. Yes	*1) first dose, date__/__/___(dd/mm/yyyy) 2) second dose, date__/__/___(dd/mm/yyyy)
		2. No	
8.	***Smoking status (current)***	1. Yes	
		2. No	
9.	***Hospital***	1. Saint Grigor Lusavorich	
		2. Nork Infectious Disease	