

Clinical Predictors of Covid-19 Mortality in a Tertiary Hospital in Lagos, Nigeria: A Retrospective Cohort Study

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Received: 09-Jul-2022;
Revision: 22-Feb-2023;
Accepted: 01-Mar-2023;
Published: 15-May-2023

ABSTRACT

Background: The predictors of mortality among patients presenting with severe to critical disease in Nigeria are presently unknown. **Aim:** The aim of this study was to identify the predictors of mortality among patients with COVID-19 presenting for admission in a tertiary referral hospital in Lagos, Nigeria. **Patients and Methods:** The study was a retrospective study. Patients' sociodemographics, clinical characteristics, comorbidities, complications, treatment outcomes, and hospital duration were documented. Pearson's Chi-square, Fischer's Exact test, or Student's *t*-test were used to assess the relationship between the variables and mortality. To compare the survival experience across medical comorbidities, Kaplan Meir plots and life tables were used. Univariable and multivariable Cox-proportional hazard analyses were conducted. **Results:** A total of 734 patients were recruited. Participants' age ranged from five months to 92 years, with a mean ± SD of 47.4 ± 17.2 years, and a male preponderance (58.5% vs. 41.5%). The mortality rate was 9.07 per thousand person-days. About 73.9% (n = 51/69) of the deceased had one or more co-morbidities, compared to 41.6% (252/606) of those discharged. Patients who were older than 50 years, with diabetes mellitus, hypertension, chronic renal illness, and cancer had a statistically significant relationship with mortality. **Conclusion:** These findings call for a more comprehensive approach to the control of non-communicable diseases, the allocation of sufficient resources for ICU care during outbreaks, an improvement in the quality of health care available to Nigerians, and further research into the relationship between obesity and COVID-19 in Nigerians.

KEYWORDS: *Clinical predictors, co-morbidity, COVID-19, Lagos, mortality*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^[1] SARS-CoV-2 is closely related to SARS-CoV-1 and is believed to be of zoonotic origin.^[2] Despite the fact that COVID-19 is primarily an infectious disease, it has been linked to a number of non-infectious consequences that are thought to be mediated by a variety of immune-related pathways.^[3-6] Similarly, while it begins with respiratory symptoms, it eventually manifests with multisystemic complications.^[7] Both the noninfectious and multisystemic consequences

of COVID-19 have considerably contributed to the mortality reported among COVID-19-admitted patients.^[5-7]


The spectrum of presentation of COVID-19 varies, and ranges from asymptomatic and mild, to severe and critical.^[8] The illness may have a mild course with little

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How to cite this article: Akase IE, Akintan PE, Otofrowei E, Olopade OB, Olorunfemi G, Opawoye A, *et al.* Clinical predictors of Covid-19 mortality in a tertiary hospital in Lagos, Nigeria: A retrospective cohort study. Niger J Clin Pract 2023;26:424-31.

Access this article online	
Quick Response Code: 	Website: www.njcponline.com
	DOI: 10.4103/njcp.njcp_454_22

or no symptoms, mimicking the common cold. In 3–4% of instances (7.4% for those over 65) the presentation requires hospitalization and intensive care unit (ICU) management. Mild cases typically recover within two weeks, however severe or critical disease may take three to six weeks.^[5,7]

According to published literature from high-income countries and some low and middle-income countries, mortality among COVID-19 patients is associated with the severity of illness, age, and the presence of co-existing morbidities.^[9-12] Given the high prevalence of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis, and malaria, as well as malnutrition and high population density in urban informal settlements with poor hygiene and sanitation, COVID-19 mortality was expected to be high in Africa. However, reported mortality rates in Africa have been lower than previously anticipated.^[13] A previous study of COVID-19- infected patients of all severity grades found that the severity of symptoms and signs at presentation, particularly in patients admitted with difficulty breathing, was the most significant clinical predictor of death.^[14] However, the predictors of mortality among patients presenting with severe to critical disease in Nigeria are presently unknown.

The aim of this study was to identify the predictors of mortality among patients with moderate to severe COVID-19 infection that was admitted at a tertiary referral hospital in Lagos, Nigeria.

METHODOLOGY

Study design and study setting

The study was an observational retrospective cohort study of all children and adults admitted to the COVID-19 Isolation and Treatment Centre at the Lagos University Teaching Hospital (LUTH), Lagos, Nigeria, from April 2020 to October 2021. The LUTH COVID-19 isolation center is located within the LUTH complex and serves both children and adults. The LUTH COVID-19 Isolation and Treatment Centre was the only one in Lagos State established inside a multi-specialty tertiary hospital, with personnel and resources to treat severe and critical COVID-19 infections, including within an intensive care unit (ICU) setup.

Study population

All patients were admitted to the isolation ward of LUTH from April 2020 through October 2021.

Study procedure

The medical records of patients admitted for COVID-19 in the LUTH COVID-19 isolation center were examined. Using a case report form [Supplementary File 1], two

members of the research team retrieved the following information from the medical records: sociodemographic information; clinical characteristics at presentation and during hospitalization; underlying chronic medical conditions and pre-existing chronic medications; hospital resource utilization or needs, such as the need for oxygen therapy, mechanical ventilation, and dialysis; duration of hospital stay; and the outcome of hospitalization.

Ethical consideration

The study got an exemption from the LUTH Health Research Ethics Committee (Approval number: LUTHHREC/EREV/0420/16) as a retrospective study and did not require informed consent because only medical information already documented in the patient's case record was reviewed. The study team did not contact the patients for the purpose of the study during the hospitalization or at any point during this study. We ensured that all extracted information bore no identifiers to the study participants; the names of participants were replaced with study ID. We ensured confidentiality by allowing access to de-identifiable extracted data to members of the study team who required access. In addition, the extracted information documented on the study proforma was stored in a locked cabinet; electronic databases derived from the study were pass-worded and access was limited to only those in the study team who needed access.

Statistical methods

Data were entered into an excel spreadsheet and then transferred to STATA version 16 (StataCorp, USA) statistical software for analysis. Data cleaning and validation were done. Descriptive statistics were conducted, and the frequency and percentages of the various outcomes was presented. Mean and standard deviation were reported for continuous variable while the median and interquartile range was reported for skewed continuous data. The association between categorical variables and each of the morbidity and mortality status was assessed using Pearson's Chi-square or Fischer's Exact test. Student's *t*-test was used to assess the difference between the mean age (and other continuous variables) of those that died and those that survived. The time-variate variable was the time to death or discharge while the outcome was mortality and those that survived were right-censored. Kaplan Meir plots and life Tables were conducted to compare the survival experience based on the various comorbidity. Univariable and multivariable Cox-proportional hazard was conducted. Variables with *P* values <0.2 were added in a backward elimination regression technique. Post regression Schoenfeld test was conducted to check for violation

of the assumptions of the model. Two models were built (Model I with age and model II did not have age). Two-tailed test of the hypothesis was assumed and a P value <0.05 was assumed to be statistically significant.

RESULTS

Sociodemographic characteristics of study participants

Between April 2020 and October 2021, a total of 734 patients were admitted into the COVID-19 ward of the Lagos University Teaching Hospital. Participants' age ranged from five months to 92 years, with a mean \pm SD of 47.4 ± 17.2 years. There was more male than female patients admitted for moderate to severe COVID-19 infection (58.5% vs. 41.5%).

Outcome of patients

As seen in Figure 1, 9.4% (95%CI: 7.43-11.85% (n = 69/734) of the individual's COVID-19 patients

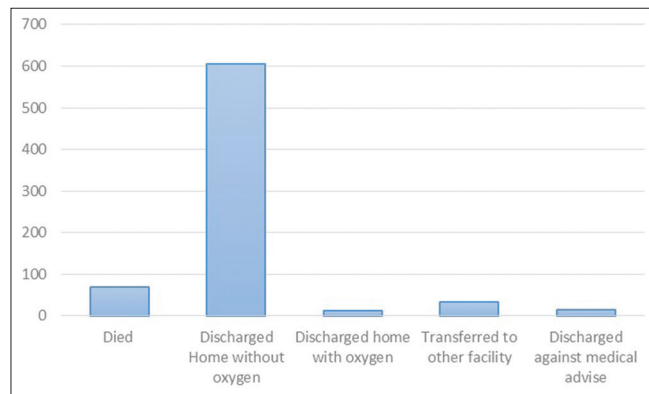


Figure 1: A bar chart of the outcome of patients admitted with COVID-19 in LUTH isolation wards from April 2020 – October 2021

died during the research period. COVID-19-infected patients who died were about 12 years older than survivors (57.06 ± 17.57 years vs. 45.39 ± 16.70 years, $P = 0.001$). Additionally, approximately 73.9% (n = 51/69) of the deceased had one or more co-morbidities, compared to 41.6% (n = 252/606) of those who were discharged. Table 1 demonstrates that diabetes mellitus, hypertension, chronic renal disease, and cancer had statistically significant associations with mortality, whereas obesity, peptic ulcer disease, Sickle cell disease, congestive heart failure, asthma, and alcohol use did not.

Survival experience of COVID-19 patients

The total period of follow-up of the COVID-19 patients was 6,728 days while the mortality rate was 9.07 per thousand person-days [Supplementary Table 1]. About 95.3% (95%CI: 94.53-97.46%) of the patients survived beyond the first day of admission while about 88.3% survived beyond 10 days of admission. Those patients who were older than 50 years, or who had diabetes, hypertension, malignancy, or were admitted into ICU had poorer survival experience [Figure 2]; Supplementary Table 2.

On univariable regression, the hazard of death among COVID-19 patients that required ICU admission was about 7-fold as compared to patients that did not require ICU admission. (HR 6.6, 95%CI: 3.53 – 12.47, P value <0.001). The hazard of death was about 3 -fold among patients with comorbidity as compared to those without comorbidity. Furthermore, patients who were about 50 years and older had about a 3-fold hazard of death from COVID-19 infection as compared to the patients who were younger than 50 years.

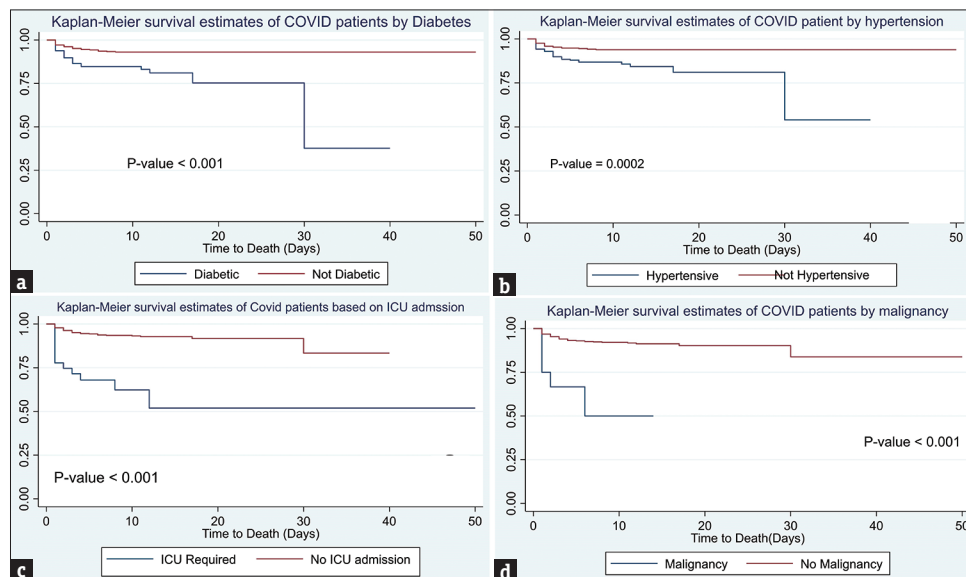


Figure 2: (a-d) Kaplan Meir Plots of the time to death of the COVID-19 participants overall and by diabetes mellitus, hypertension, malignancy, and intensive care unit admission status

Table 1: Association between co-morbidities and survival among COVID-19 patients

Characteristics (Co-morbidity)	Discharged home without oxygen	Dead	Total	P
Age (mean±SD) Years	45.39±16.70	57.06±17.57	46.54±17.13	<0.0001
<50	352 (58.1)	20 (28.9)	372 (55.1)	<0.001
≥50	254 (41.9)	49 (70.1)	303 (44.9)	
Morbidities				
Yes	252 (41.6)	51 (73.9)	303 (44.9)	<0.001
No	354 (58.4)	18 (26.1)	372 (55.1)	
Diabetes Mellitus				
Yes	94 (15.5)	29 (42.0)	123 (18.2)	<0.0001
No	512 (84.5)	40 (58.0)	552 (81.8)	
Hypertension				
Yes	199 (32.8)	41 (59.4)	240 (35.6)	<0.001
No	407 (67.2)	28 (40.6)	435 (64.4)	
CKD				
Yes	5 (0.82)	3 (4.3)	8 (1.2)	0.041
No	553 (99.2)	66 (95.7)	667 (98.8)	
Obesity				
Yes	11 (1.8)	4 (5.8)	15 (2.2)	0.111
No	595 (98.2)	65 (94.2)	660 (97.8)	
SCD				
Yes	5 (0.8)	2 (2.9)	7 (1.0)	0.400
No	601 (99.2)	67 (97.1)	668 (99.)	
HIV Status				
Yes	6 (1)	2 (2.9)	8 (1.2)	0.458
No	600 (99)	67 (97.1)	667 (98.8)	
Asthma status				
Yes	16 (3.1)	0 (0.00)	16 (2.4)	0.383
No	590 (96.9)	69 (100.00)	659 (97.6)	
Malignancy				
Yes	7 (1.2)	7 (10.1)	14 (2.1)	<0.001
No	599 (98.8)	62 (89.9)	661 (97.9)	
Heart failure				
Yes	10 (1.7)	4 (5.8)	14 (2.1)	0.100
No	596 (98.3)	65 (94.2)	599 (97.9)	
Cerebrovascular accident				
Yes	6 (1)	4 (5.8)	10 (1.5)	0.035
No	600 (99)	65 (94.2)	665 (98.5)	
Peptic Ulcer Disease				
Yes	20 (3.3)	2 (2.9)	22 (3.3)	1.000
No	586 (96.7)	67 (97.1)	653 (96.7)	
Hemiplegia				
Yes	4 (0.7)	3 (4.3)	7 (1)	0.078
No	602 (99.3)	66 (95.7)	668 (99)	
ICU requirement				
Yes	8 (1.5)	17 (24.6)	25 (3.7)	<0.001
No	597 (98.5)	22 (75.4)	650 (96.3)	
Alcohol use				
No	572 (94.4)	65 (93.55)	637 (94.4)	0.695
Yes	34 (5.6)	4 (6.45)	38 (5.6)	

After multivariable regression, the hazard of death from COVID-19 infection increases by about 3% for every annual increase in age [Table 2]. After correcting for confounding variables, patients with Diabetes mellitus had about 2- a fold hazard of death as compared to

patients who were not diabetic (Adjusted HR: 2.4, 95% CI: 1.30- 4.51, *P* value = 0.006). Likewise, patients with a history of hypertension or malignancy had about 2-fold and 8.5-fold hazard of death as compared to those without hypertension or malignancy respectively.

Table 2: Univariable and Multivariable Cox proportional hazard ratio of the association between age and comorbidities and mortality from COVID-19 patients (Model II)

Characteristics	HR	95%CI	P	Adjusted HR	95%CI	P
Age	1.04	1.02-1.06	<0.001	1.03	1.01-1.05	0.012
<50	1.00	Reference	Reference			
≥50	2.83	1.62-4.93	<0.001			
Morbidity						
None	1.00	Reference	Reference			
Yes	3.20	1.83-5.60	<0.001			
Diabetes Mellitus						
Non-DM	1.00	Reference	Reference	1.00	Reference	Reference
DM	2.92	1.72-4.95	<0.001	2.04	1.10-3.79	0.024
Hypertension history						
Non-hypertensive	1.00	Reference	Reference	1.00	Reference	Reference
Hypertension	2.60	1.54-4.38	<0.001	1.24	0.63-2.44	0.527
Malignancy						
No history of malignancy	1.00	Reference	Reference	1.00	Reference	Reference
History of malignancy	7.58	3.24-17.73	<0.001	8.11	1.86-14.04	0.002
Obesity						
Non-obese	1.00	Reference	Reference	1.00	Reference	Reference
Obese	2.60	0.80-8.45	0.112	2.70	0.82-8.82	0.100
History of CKD						
None	1.00	Reference	Reference			
CKD	4.02	0.98-16.55	0.054			
History of SCD						
Non-SCD	1.00	Reference	Reference			
Sickle cell disease	2.41	0.33-17.44	0.383			
HIV status						
HIV Negative	1.00	Reference	Reference			
HIV Positive	1.62	0.22-11.69	0.634			
History of Congestive cardiac failure						
No CCF	1.00	Reference	Reference			
Congestive cardiac failure	1.40	0.19-10.10	0.741			
Peptic Ulcer Disease						
No	1.00	Reference	Reference			
Yes	0.60	0.08-4.34	0.613			
Hemiplegia						
No	1.00	Reference	Reference			
Yes	4.26	1.04-17.51	0.044			
Alcohol ingestion						
No	1.00	Reference	Reference			
Yes	0.94	0.22-3.95	0.934			
ICU Admission						
ICU not necessary	1.00	Reference	Reference			
ICU Necessary	6.64	3.53-12.47	<0.001			

The hazard of death among obese patients was not statistically different from the hazard of death among non-obese patients after correcting for confounding variables.

DISCUSSION

Principal findings

In this retrospective cohort study, the medical records of 734 COVID patients admitted to a referral facility

were examined to determine the mortality rate and the determinants of mortality. The study found a 9.4 percent death rate. In our patient cohort, age, diabetes, hypertension, chronic renal disease, cancer, and ICU admission were substantially linked with the hazard of death.

Strengths and limitations

The comparatively large sample size of patients presenting with the severe and critical diseases is

the primary strength of this study. Lagos State is the epicenter of the COVID-19 pandemic in Nigeria; and with LUTH being the largest referral center for cases that were complicated or required multi-specialist care, this cohort represented the largest single-center review of patients in Nigeria with severe and critical COVID-19.

However, because this is a single-center study, it has limitations. It is also retrospective in nature and is hospital-based. Furthermore, the follow-up duration was limited to the time spent in the hospital. There was no information on what happened to patients after they were discharged, transferred to another facility, or discharged against the medical recommendations.

Comparison with other studies

The present study revealed a mortality rate of 9.4%, which was higher than the global death rate for COVID-19,^[15] as well as the death rates reported for the general population of Lagos State^[16] and Nigeria.^[17] However, our hospital's mortality rate was comparable to that of other referral hospitals that also admitted a large proportion of moderate to severe cases of COVID-19 patients as we did at our center.^[18-20]

Globally, there has been a significant link between COVID-19-related death and increasing age, particularly among people over the age of 65.^[21,22] In our cohort of patients, the risk of death increased by about 3% as they got older. It was discovered that people over the age of 50 had a higher risk of dying from COVID-19, which was consistent with data from other low-resource countries.^[23-25] Low- and middle-income countries (LMICs) are believed to have a greater proportion of COVID-19 deaths at younger ages than high-income countries (HICs), with COVID-19 age-mortality curves in developing nations generally being flatter.^[25]

Numerous studies have also demonstrated the association between mortality and the presence of comorbidities among COVID-19 patients.^[14,18-20] Diabetes mellitus,^[9,14,18] hypertension,^[16,19] chronic kidney disease,^[26,27] and cancer^[28,29] have been shown to be strong predictors of COVID-19 death. This is consistent with the results of our study. As was also found in this study, no significant association was found between mortality and well-controlled asthma.^[30] It is also believed that SCD is not an independent risk factor for COVID-19 death, as the haemoglobin genotype does not appear to be associated with the severity of COVID-19 disease.^[31] Obesity was not a risk factor for mortality among our participants. This is contrary to research elsewhere, which has shown that obesity may be able to predict the risk and outcome for COVID-19 patients younger than

60 years of age.^[32] Renal insufficiency, cardiovascular disease, Type 2 diabetes, certain cancers, and endothelial dysfunction are more prevalent among obese individuals.^[33] These conditions increase the severity and mortality of COVID-19. In addition, obesity was believed to act independently to worsen the prognosis of COVID-19 patients, in part because adipose tissue impacts immune function.^[34] Adipose tissue is a crucial endocrine organ that secretes Adipokines, Chemokines, and Cytokines, which influence metabolism and the immune system.^[33-36] Thus, it is difficult to explain our finding that there is no correlation between obesity and COVID-19 mortality. More research is required to determine the link between obesity and COVID-19 mortality in Nigeria.

The association between the requirement for ICU care in our facility and death is consistent with findings elsewhere, which has been thought to be a reflection of the severity of COVID-19.^[37,38] A meta-analysis to evaluate mortality rates of patients with COVID-19 in the ICU suggested that the poor outcomes seen in various studies may be related to the rationing of resources in overwhelmed ICUs, and not primarily to the severity of the underlying illness.^[39] This was also observed in another study from Sweden that found higher death rates among COVID-19 patients admitted in the setting of increased admissions than when admission rates were lower.^[40]

Interpretation of findings and implications

The predictors of mortality as found in our study demonstrate the similarity of the pattern of mortality determinants among patients with severe disease in both low- and high-income countries. However, there are subtle differences in our setting, both in terms of the lower absolute number of COVID-19 deaths and the relatively younger age of onset associated with increased mortality.

The association between lower at-risk age and COVID-19 mortality observed in this study reflects the pattern among LMICs and is believed to be a result of the Gompertz effect, which essentially means that population differences in mortality reflect the underlying population health and the quality of health care available to them.^[41] The life expectancy in Nigeria is about 54 years, which is consistent with the finding in this study.^[42]

In addition, the lack of a significant association between obesity and COVID-19 deaths among these patients appears to support the notion that obesity acts within a structure of added insult, such as an increased cardiovascular risk or an unfavorable immune

environment.^[33,34] It is widely believed that common immunosuppressive conditions (such as malnutrition, tuberculosis, helminthic infections, and anemia) among Africans may provide protection against COVID-19,^[43,44] as it is well known that hyperinflammation and other immunopathologic mechanisms play crucial roles in adverse outcomes among COVID-19-infected patients who are hospitalized. This postulation needs to be investigated further.

CONCLUSION

The study found that the mortality rate at a tertiary referral center was greater than that of the general Nigerian populace. Age, diabetes mellitus, hypertension, chronic renal disease, malignancy, and the necessity for ICU hospitalization were significantly associated with mortality. These findings call for a better approach to the control of non-communicable diseases (NCDs), as they have been shown to impact negatively during infectious disease outbreaks. Secondly, it is now clear that, as part of our epidemic preparedness planning, deliberate attempts must be made to ensure adequate resources are allocated to ICU capacity to ramp up care in the case of an outbreak. In the longer term, the quality of health care that is available to Nigerians must improve, to both increase the life expectancy of Nigerians, and also ensure a more robust response to emergencies. Further research is needed to identify the relationship between obesity and COVID-19 among Nigerian patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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**Supplementary Table 1: Life Table of
COVID-19 patients**

Time	Beginning Total	Fail	Net Lost	Function	95% CI	
1	670	25	16	0.9627	0.9453	0.9746
2	629	10	14	0.9474	0.9275	0.9619
3	605	9	31	0.9333	0.9114	0.9499
4	565	5	23	0.9250	0.9020	0.9428
5	537	1	48	0.9233	0.9000	0.9413
6	488	4	35	0.9157	0.8913	0.9349
7	449	1	37	0.9137	0.8889	0.9331
8	411	1	41	0.9115	0.8863	0.9313
9	369	0	46	0.9115	0.8863	0.9313
10	323	1	71	0.9087	0.8828	0.9290
11	251	1	42	0.9050	0.8781	0.9263
12	208	1	36	0.9007	0.8722	0.9231
13	171	0	28	0.9007	0.8722	0.9231
14	143	0	19	0.9007	0.8722	0.9231
15	124	0	18	0.9007	0.8722	0.9231
16	106	0	13	0.9007	0.8722	0.9231
17	93	1	11	0.8910	0.8552	0.9184
18	81	0	7	0.8910	0.8552	0.9184
19	74	0	7	0.8910	0.8552	0.9184
20	67	0	11	0.8910	0.8552	0.9184
21	56	0	14	0.8910	0.8552	0.9184
22	42	0	2	0.8910	0.8552	0.9184
23	40	0	4	0.8910	0.8552	0.9184
24	36	0	7	0.8910	0.8552	0.9184
25	29	0	2	0.8910	0.8552	0.9184
27	27	0	4	0.8910	0.8552	0.9184
28	23	0	5	0.8910	0.8552	0.9184
29	18	0	4	0.8910	0.8552	0.9184
30	14	1	6	0.8274	0.6590	0.9175
31	7	0	1	0.8274	0.6590	0.9175
32	6	0	1	0.8274	0.6590	0.9175
34	5	0	1	0.8274	0.6590	0.9175
35	4	0	1	0.8274	0.6590	0.9175
40	3	0	2	0.8274	0.6590	0.9175
50	1	0	1	0.8274	0.6590	0.9175

Supplementary Table 2: Survival experience age and morbidity types

Characteristics	Time at risk	Mortality rate	Subjects	25%	50%	75%
Overall	6,728	0.0090666	670	.	.	.
Age						
<50	3,951	0.0045558	355	.	.	.
≥50	2,662	0.015402	304	.	.	.
Diabetes Mellitus						
Yes	1,177	0.0195412	129	30	30	.
No	5,384	0.006315	521	.	.	.
Hypertension						
Yes	2,156	0.0157699	242	30	.	.
No	4,420	0.0054299	411	.	.	.
Obesity						
Obese	148	0.0202703	13	.	.	.
Non-obese	6,118	0.0081726	607	.	.	.
Malignancy						
Malignancy	71	0.084507	12	1	6	.
Non Malignancy	6,393	0.0079775	629	.	.	.
ICU Admission						
ICU Required	267	0.0486891	36	2	.	.
ICU not required	6,148	0.0066688	599	.	.	.