Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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One-year outcomes of invasively managed acute coronary syndrome patients with COVID-19

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ABSTRACT

Background: There is a limited data about the one-year outcomes of patients diagnosed with acute coronary syndrome (ACS) and coronavirus disease 2019 (COVID-19).
Objectives: To assess one-year mortality of invasively managed patients with ACS and COVID-19 compared to ACS patients without COVID-19.
Methods: In our investigation, we defined the study time period as April 30 through September 1, 2020. The control groups consisted of ACS patients without COVID-19 at the same time period and ACS patients prior to the pandemic, within the same months as those of the study. COVID-19 infection was confirmed in all participants utilizing real-time polymerase chain reaction testing.
Results: This investigation examined 721 ACS participants in total. Among the participants, 119 patients were diagnosed with ACS and COVID-19, while 149 were diagnosed with ACS and without COVID-19. The other 453 ACS participants were diagnosed before the outbreak of the pandemic, within the same months as those of the study. One-year mortality rates were higher in the ACS participants with COVID-19 than in the ACS participants without COVID-19 and the pre-COVID-19 ACS participants (21.3% vs. 6.5% vs. 6.9%, respectively). An ACS along with COVID-19 was the only independent predictor of one-year mortality (HR=2.902, 95%CI=1.211–6.824, P = 0.018). According to the Kaplan-Meier survival curves, patients with ACS and COVID-19 had a lower chance of survival in the short-term and one-year periods.
Conclusion: This is believed to be the first study to report that ACS patients with COVID-19 had higher one-year risk of mortality compared to ACS patients without COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is a viral infection caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2).[1] After the identification of the first case in December 2019 in Wuhan, China, the infection spread globally, resulting in a pandemic.[1] Although the lungs are predominantly affected by COVID-19 infection, the virus can also cause acute coronary syndrome (ACS).[2] Several mechanisms for acute myocardial damage in patients infected with the virus have been proposed, including an atherosclerotic plaque rupture triggered by endothelial cell injury, an elevated inflammatory state, and a cytokine storm.[3] Furthermore, cardiac injury is commonly detected in COVID-19 patients, as demonstrated by natriuretic peptide and troponin elevation, and such patients have poorer outcomes than those without myocardial damage.[4,5]

Early studies found that patients diagnosed with ACS and concomitant COVID-19 infection had higher in-hospital and short-term (30-days) death rates than ACS patients without COVID-19 infection.[6,7] However, there is a limited data in the existing literature about the one-year outcomes of individuals diagnosed with ACS and concomitant COVID-19 disease. As a result, the purpose of this research was to assess the one-year mortality of invasively managed individuals with both ACS and COVID-19 compared to ACS patients without COVID-19.

Methods

Study participants

The records of ACS patients who were diagnosed either with an ST elevation myocardial infraction (STEMI) or a non-ST elevation myocardial infraction (NSTEMI) in a tertiary center were analyzed in this

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study. The diagnoses of STEMI and NSTEMI were defined in accordance with the current guidelines.[8,9] We defined the study time period as April 30 through September 1, 2020. The control group consisted of ACS patients who had not been infected with COVID-19 at the same time period. In addition, data from ACS patients prior to the outbreak of the pandemic within the same months as those of the study were analyzed. These patients were also referred to as the control group.

In this study, we only analyzed the data of ACS patients who underwent coronary angiography (CAG). In addition, patients treated with thrombolytic treatment were excluded (n = 2 participants). COVID-19 infection was confirmed in all participants utilizing real-time polymerase chain reaction testing as well as chest X-ray or computed tomography. The following data were collected for each patient; baseline characteristics (age, sex, and body mass index) and co-morbidities (e.g., hypertension, diabetes, hyperlipidemia, or coronary artery disease). All laboratory test results, including lipid profiles, C-reactive protein (CRP), and cardiac troponin I levels at admission, were obtained from a hospital laboratory database. The study was approved by both the Ministry of Health (No. 2021–09–04T06_44_56) and the Local Ethics Committee (No. 2021/20), and it was carried out according to the Helsinki Declaration.

Interventional procedure

In all participants, invasive angiography was accomplished via the femoral or radial artery, and all interventions were done by skilled operators using established interventional approaches. All patients received 300 mg of acetylsalicylic acid and a loading dose of P_2Y_{12} inhibitors before the CAG operation. The culprit lesions were managed with balloon angioplasty and/or stent deployment, as suggested by the current guidelines. Two qualified operators who were anonymized to the medical data meticulously reviewed all patients' angiographic data.

Study outcomes

In-hospital mortality referred to deaths that occurred during a hospital stay, whereas short-term mortality referred to deaths that occurred within 30 days following admission. One-year mortality was defined as deaths that occurred after 30 days. The National Death Registry System data was assessed to determine short-term and one-year survival rates.

Statistical analysis

R software, version 3.6.3 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria) and GraphPad Prism 8 for Macos (GraphPad Software) was used for the statistical analyses. To assess whether the variables were normally distributed, the Kolmogorov-Smirnov test was used. The continuous variables were denoted as mean (SD) with normal distribution and as median (interquartile range (IQR)) with non-normal distribution. Numbers and percentages were used to present the categorical data. The categorical variables were compared between the groups using the $\chi 2$ test or Fisher-Freeman-Halton exact test. When a statistical significance of homogeneity was detected, we used multiple z-tests of two proportions for post-hoc comparisons between the subgroups.

To compare continuous variables between groups, either the one-way ANOVA or Kruskal-Wallis test was employed, where appropriate. For post-hoc comparisons of continuous variables between subgroups, Tukey post hoc analysis or Dunn's procedure with Bonferroni correction was used. Multivariable Cox regression analysis with clinically relevant variables was performed for detecting independent predictors of in-hospital, short-term, and one-year mortality with the same covariates in three different models. To avoid overfitting, Firth's penalized likelihood bias reduction was used in regression models. Mullticollinearity was assessed using VIF (variance inflation factor >3) and tolerance (<0.1) values. The Kaplan Meier survival curves were created to compare short-term and one-year mortality rates between subgroups of the study population. In the presence of a statistically significant difference in the log-rank test, a pairwise comparison was used for subgroup analysis. The findings were analyzed using a 95% confidence interval (CI) and a significance threshold of P value < 0.05.

Results

This study examined a total of 721 participants of ACS. Among the participants, 119 patients were diagnosed with ACS and COVID-19, while 149 were diagnosed with ACS and without COVID-19. The other 453 ACS participants were diagnosed before the outbreak of the pandemic, within the same months as those of the study. During the time of the pandemic, the number of patients who were diagnosed with ACS dropped by 41% compared to the same period of time during the previous year (**Fig. 1A**).

The baseline demographics, laboratory findings, and prior treatments of all participants are presented in **Table 1**. There was no significant difference among the groups in relation to age, ethnicity, or body mass index. The clinical presentation of STEMI or NSTEMI was comparable among the groups. With regard to comorbidities, we found that all groups were similar. When compared to the ACS participants without COVID-19, those with COVID-19 showed significantly higher white blood cell and neutrophil counts and levels of creatinine, CRP, triglyceride, and troponin I. Furthermore, ACS patients who also had COVID-19 had lower lymphocyte counts. In terms of their previous treatments, the groups were comparable.

Table 2 illustrates the angiographic outcomes and mortality rates for each group. There were no substantial differences with respect to infarct-related arteries. Among the ACS participants with COVID-19, multi-vessel coronary artery disease was frequently detected. The interventional therapies, including percutaneous transluminal coronary angioplasty (PTCA), direct stent implantation, and PTCA + stent implantation, did not differ across the groups. At the time of admission, the participants involving ACS patients who had COVID-19 had higher Killip classes greater than 2 at admission. Inotropic support and the need for intubation were also more frequent in this group.

The time from the onset of symptoms to percutaneous coronary intervention (PCI) was considerably longer in the ACS participants with COVID-19, as shown in **Fig 2**. In-hospital, short-term, and one-year mortality rates were higher in the ACS participants with COVID-

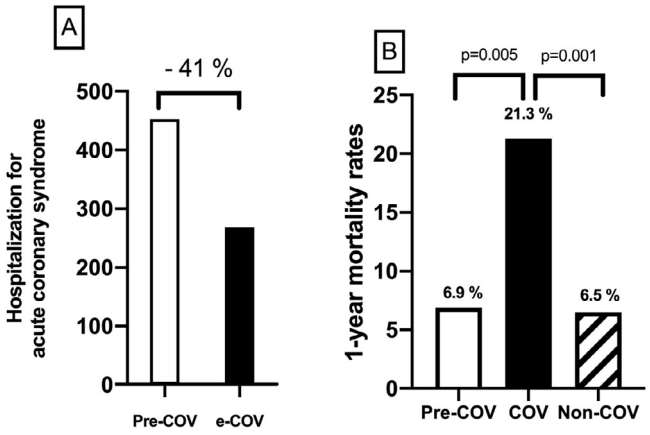

Fig. 1. Comparison of ACS admission rates during pandemic and prepandemic period throughout same period 1-year mortality rates of ACS patients with and without COVID-19.
Abbreviations: ACS, acute coronary syndrome; COVID-19, coronavirus disease 2019

Table 1
Baseline characteristics, laboratory results and previous medications for all participants included in the study.

	ACS with COVID-19[1]	ACS without COVID-19[2]	Pre-COVID-19 ACS[3]	P value	Post-Hoc comparison		
	(*n* = 119)	(*n* = 149)	(*n* = 453)		1–2	1–3	2–3
Age, years	64.7(12.8)	63.4(13.7)	62.1(11.8)	0.107	–	–	–
Male gender, n (%)	66(55.5)	80(53.7)	260(57.4)	0.071	–	–	–
BMI, kg/m^2	25.3(2.5)	25.2(2.4)	25.7(2.5)	0.058	–	–	–
Clinical presentation							
STEMI	66(55.5)	66(44.3)	208(45.9)	0.131	–	–	–
NSTEMI	53(44.5)	83(55.7)	245(54.1)		–	–	–
Risk factors							
Hypertension, n (%)	59(49.6)	80(53.7)	217(47.9)	0.471	–	–	–
Diabetes, n (%)	34(28.6)	36(24.2)	140(30.9)	0.288	–	–	–
Previous CAD, n (%)	23(19.3)	30(20.1)	102(22.5)	0.679	–	–	–
CHF, n (%)	21(17.6)	20(13.4)	66(14.6)	0.605	–	–	–
CVA, n (%)	6(5)	4(2.7)	36(7.9)	0.06	–	–	–
Hyperlipidemia, n (%)	24(20.2)	35(23.5)	81(17.9)	0.316	–	–	–
COPD, n (%)	19(16)	18(12.1)	63(13.9)	0.658	–	–	–
Smoking, n (%)	51(42.9)	74(49.7)	182(40.2)	0.127	–	–	–
Laboratory data							
WBC, $10^3\mu$L	11.8(9.9–15.9)	10.4(8.2–13.2)	9.6(7.5–13.5)	<0.001	0.004	<0.001	0.642
Neutrophil, $10^3\mu$L	8.2(5.8–12.2)	6.1(3.9–9.3)	6.3(4.2–8.8)	<0.001	<0.001	0.003	1.000
Lymphocyte, $10^3\mu$L	0.9(0.5–1.8)	1.2(0.7–2)	1.2(0.8–2)	0.001	0.072	<0.001	0.939
Creatinine, mg/dL	1.1(0.9–1.3)	0.9(0.7–1.1)	1(0.8–1.1)	<0.001	<0.001	<0.001	0.08
CRP, mg/dL	35(12–95)	9(7–11)	7(5–8)	<0.001	<0.001	<0.001	<0.001
LDL cholesterol, mg/dL	117(46)	120(45)	114(42)	0.418	–	–	–
Triglyceride, mg/dL	114(79–168)	98(70–160)	110(85–164)	0.009	0.039	1.000	0.012
HDL cholesterol, mg/dL	43(11)	42(13)	44(10)	0.051	–	–	–
Troponin I, ng/mL	12(6–18)	11(2–14)	7(4–14)	<0.001	<0.001	<0.001	1.000
Previous medication							
ASA, n (%)	26(21.8)	40(26.8)	112(24.7)	0.641	–	–	–
Antiplatelet, n (%)	8(6.7)	9(6)	39((8.6)	0.535	–	–	–
Beta blockers, n (%)	29(24.4)	46(30.9)	119(26.3)	0.433	–	–	–
CC blockers, n (%)	14(11.8)	28(18.8)	57(12.6)	0.128	–	–	–
ACE inh/ARBs, n (%)	46(38.7)	63(42.3)	197(43.5)	0.637	–	–	–
Statin, n (%)	20(16.8)	26(17.4)	70(15.5)	0.825	–	–	–

Abbreviations: BMI, body mass index; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; CRP, C-reactive protein; LDL, low density lipoprotein; HDL, high density lipoprotein; ASA, acetylic salic acid; CC, calcium channel; Ace inh/ARBs, angiotensinogen converting enzyme/ angiotensinogen receptor blockers.

Table 2
Angiographic data and in-hospital, short- and long-term mortality rates of all participants included in the study.

	ACS with COVID-19[1]	ACS without COVID-19[2]	Pre-COVID-19 ACS[3]	P value	Post-Hoc comparison		
	(*n* = 119)	(*n* = 149)	(*n* = 453)		1–2	1–3	2–3
Culprit lesion, n (%)					–	–	–
LAD	43(36.1)	64(43)	197(43.5)		–	–	–
Cx	40(33.6)	49(32.9)	149(32.9)		–	–	–
RCA	29(24.4)	34(22.8)	98(21.6)	0.071	–	–	–
LMCA	2(1.7)	0(0)	0(0)		–	–	–
Graft	5(4.2)	2(1.3)	9(2)		–	–	–
Multivessel, n (%)	38(31.9)	36(24.2)	166(36.6)	0.018	0.606	1.000	0.021
Procedure, n (%)							
Only PTCA	1(0.8)	5(3.4)	25(5.5)		–	–	–
Stent	26(21.8)	25(16.8)	65(14.3)	0.128	–	–	–
PTCA+stent	86(72.3)	111(74.5)	329(72.6)		–	–	–
CABG	6(5)	8(5.4)	34(7.5)		–	–	–
LV ejection fraction,%	44(34–54)	42(33–57)	46(36–56)	0.084	–	–	–
Killip status > II	26(21.8)	19(12.8)	35(7.7)	<0.001	0.209	<0.001	0.269
Time to PCI, hours	17(13–20)	14(11–17)	5(4–6)	<0.001	0.124	<0.001	<0.001
Inotropic support, n (%)	15(12.6)	12(8.1)	24(5.3)	0.02	0.915	0.027	0.906
Intubation rate, n (%)	19(16)	8(5.4)	10(2.2)	<0.001	0.024	<0.001	0.274
In-hospital mortality, n (%)	21(17.6)	9(6)	19(4.2)	<0.001	0.015	<0.001	1.000
30-days mortality, n (%)	25(21)	11(7.4)	32(7.1)	<0.001	0.006	<0.001	1.000
1-year mortality, n (%)	20(21.3)	9(6.5)	29(6.9)	<0.001	0.001	0.005	1.000

Abbreviations: LAD, left anterior descending artery; Cx, circumflex artery; RCA, right coronary artery; LMCA, left main coronary artery; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; LV, left ventricle; PCI, percutaneous coronary intervention.

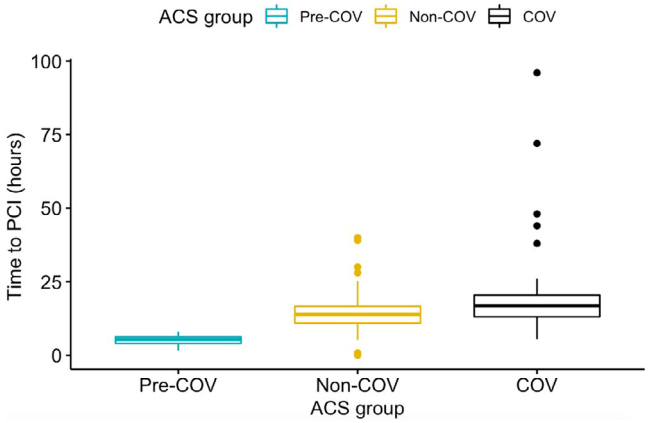

Fig. 2. Comparison of time to PCI in ACS patients with and without COVID-19. **Abbreviations**: PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; COVID-19, coronavirus disease 2019

19 than in the ACS participants without COVID-19 and the pre-COVID-19 ACS participants [n = 21 (17.6%) vs. n = 9 (6%) vs. n = 19 (4.2%), n = 25 (21%) vs. n = 11 (7.4%) vs. n = 32 (7.1%), and n = 20 (21.3%) vs. n = 9 (6.5%) vs. n = 29 (6.9%), respectively] (**Fig. 1B**).

In the multivariable Cox regression model, inotropic support, Killip class > II, and ACS with COVID-19 (HR=4.594, 95% CI=1.672–13.018, P = 0.003) all independently predicted in-hospital deaths (**Table 3**). In the multivariate Cox regression model, Killip class > II and ACS with COVID-19 (HR=3.528, 95% CI=1.411–9.090, P = 0.004) were linked to short-term mortality. An ACS along with COVID-19 was the only independent predictor of one-year mortality (HR=2.902, 95% CI=1.211–6.824, P = 0.018). According to the Kaplan-Meier survival curves, patients with ACS and COVID-19 had a lower chance of survival in the short-term and one-year periods (**Figs. 3 and 4**).

Table 3
Multivariable COX regression analysis for independent predictors of in-hospital, short- and long-term mortality.

	HR (95%CI)	P value
In-hospital mortality		
Time to PCI	0.967(0.899–1.019)	0.268
Inotropic support	2.832(1.151–6.368)	0.025
Killip status > II	2.392(1.114–4.863)	0.026
Troponin I	0.991(0.945–1.037)	0.704
CRP	1.004(0.999–1.009)	0.073
ACS groups		
Reference (Pre-COVID-19 ACS)	–	–
ACS without COVID-19	1.817(0.674–4.782)	0.236
ACS with COVID-19	4.594(1.672–13.018)	0.003
30-day mortality		
Time to PCI	0.966(0.905–1.012)	0.179
Inotropic support	2.112(0.913–4.487)	0.078
Killip status > II	2.261(1.154–4.249)	0.018
Troponin I	1.028(0.988–1.068)	0.165
CRP	1.005(0.999–1.009)	0.057
WBC	0.947(0.887–1.004)	0.069
ACS groups		
Reference (Pre-COVID-19 ACS)	–	–
ACS without COVID-19	1.398(0.579–3.320)	0.588
ACS with COVID-19	3.528(1.411–9.090)	0.004
1-year mortality		
Time to PCI	1.004(0.964–1.036)	0.808
Inotropic support	1.939(0.831–4.144)	0.120
Killip status > II	1.843(0.856–3.702)	0.114
Troponin I	0.994(0.951–1.036)	0.762
CRP	1.002(0.997–1.007)	0.373
WBC	0.967(0.905–1.024)	0.261
ACS groups		
Reference (Pre-COVID-19 ACS)	–	–
ACS without COVID-19	0.905(0.382–2.006)	0.809
ACS with COVID-19	2.902(1.211–6.824)	0.018

Abbreviations: ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CRP, C-reactive protein; WBC, white blood cell.

Discussion

To our knowledge, the literature was lacking a one-year assessment study of ACS patients presenting with COVID-19. This study might be one of the first to assess one-year mortality outcomes of ACS patients with COVID-19, showing that such patients had higher mortality rates in this period.

Since the pandemic began, there have been several studies that have demonstrated the tendency of ACS patients to present to the emergency services (ES) at relatively long periods of time after they became ill or not to present at all. It is interesting to note that ACS admissions decreased dramatically throughout the world during the initial period of the pandemic,[10] and this might be because of fears of contracting COVID-19 during ES visits.[11,12] This decrease is consistent with our findings, as we reported a 41% decrease in ACS patients who presented to the ES.

Our study also found that the times from the onset of symptoms to PCI were higher in the COVID-19 group than among those who did not have the disease. This may have been caused by the delays in patients presenting to the ES or in physicians being reluctant to perform invasive procedures and deciding to treat patients with medical therapy alone until they were deemed to be free of COVID-19.[10] Rashid et al. reported similar findings, with dual antiplatelet therapy (DAPT) initiation rates that were even lower in the patients with ACS and COVID-19.[13] However, the increases in the times from the onset of symptoms to PCI were not associated with higher one-year mortality rates in the group that had ACS with COVID-19.

The main pathophysiological mechanism in the development of ACS is the rupture of atherosclerotic plaque and the aggregation of blood components on top of the rupture site. Viral infections in particular, including COVID-19, may precipitate this process.[14] In addition, COVID-19 infection can have deleterious effects for ACS patients. For example, the infection can boost the host inflammatory response (the cytokine storm) and this might lead to complex clinical syndrome.[14] Anti-virus treatment can also cause some adverse effects and, finally, epidemic control for patients with COVID-19 and ACS can cause delayed or complicated clinical protocols.

In our investigation, the in-hospital and short-term mortality rates of ACS patients with COVID-19 were higher than those of ACS patients without COVID-19, and this is consistent with the current literature. For example, Saad et al. found that the mortality rates for in-hospital and out-of-hospital STEMI patients with COVID-19 were higher than for their non-COVID-19 counterparts.[15] Moreover, Rashid et al. reported that the in-hospital and 30-day mortality rates of ACS patients with COVID-19 were three and six times higher than those of their non-COVID-19 counterparts.[13] We also found that ACS patients with COVID-19 had higher in-hospital and short-term mortality rates than those without COVID-19. However, the information about the one-year prognosis for ACS patients with COVID-19 was limited. In our analysis, ACS patients with COVID-19 had worse outcomes than ACS patients without COVID-19. Approximately one out of every five ACS patients who had COVID-19 died during the one-year study period, and these patients had a risk of long-term death that was 2.9 times higher than that of the overall cohort. Furthermore, having COVID-19 infection at the same time as ACS was the sole independent predictor of one-year death. Indeed, the increase in one-year mortality may be due to the COVID-19 infection itself. The higher Killip classes at presentation, along with elevated troponin concentration levels in those who had both COVID-19 and ACS, may indicate that there was larger myocardial damage in this group.[16] It is commonly accepted that an increase in cardiac troponin levels is linked to poor outcomes in COVID-19 patients.[5,17] However, it is questionable whether the increases in cardiac troponins are due to

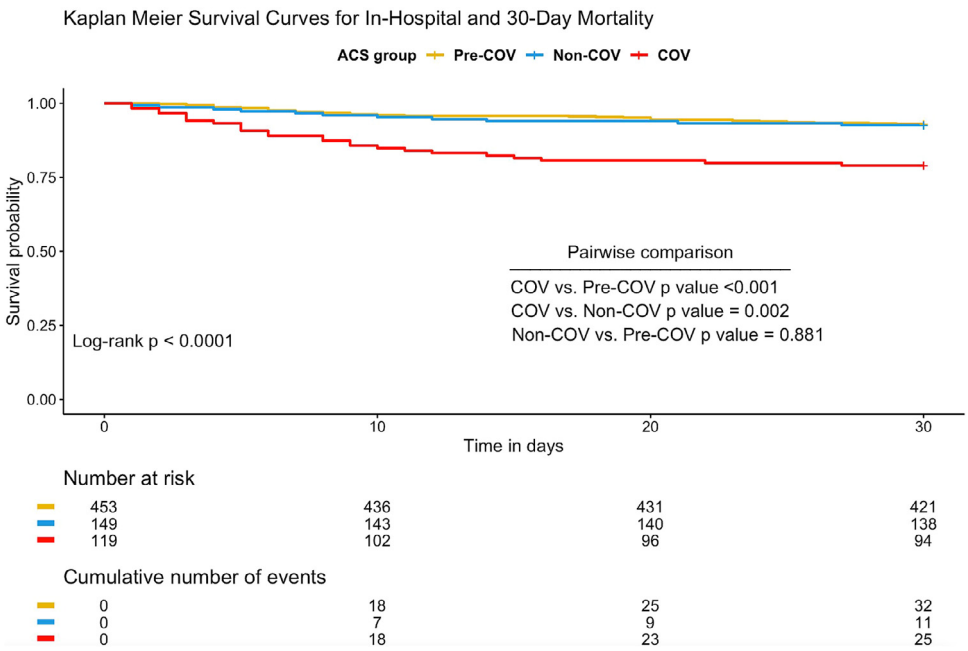

Fig. 3. In-hospital and short-term Kaplan Meir survival analysis of ACS patients with and without COVID-19. **Abbreviations**: ACS, acute coronary syndrome; COVID-19, coronavirus disease 2019

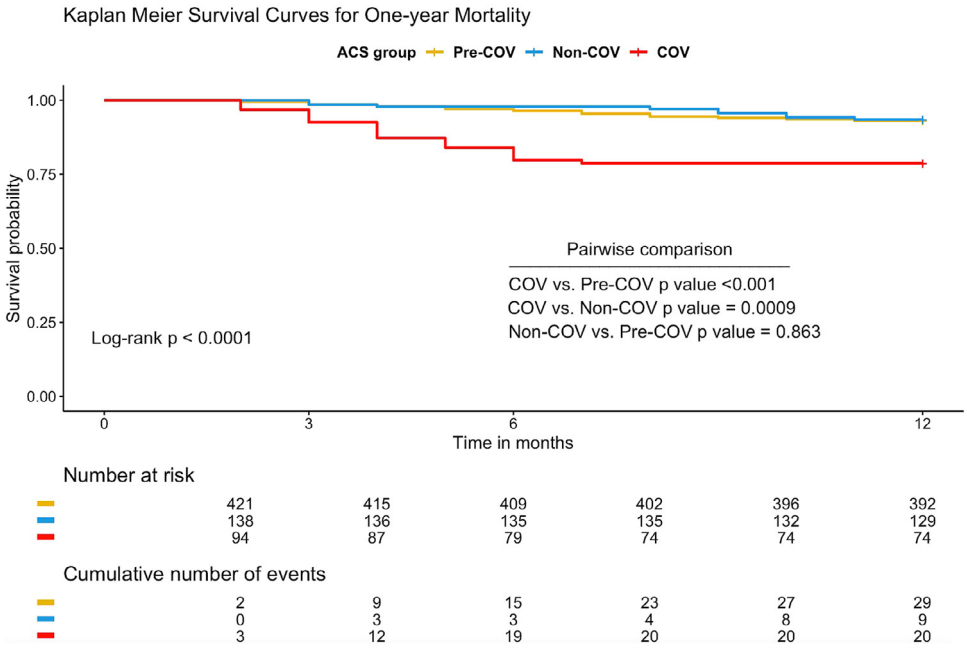

Fig. 4. Long-term Kaplan Meir survival analysis of ACS patients with and without COVID-19. **Abbreviations**: ACS, acute coronary syndrome; COVID-19, coronavirus disease 2019

viral myocarditis, to plaque rupture caused by virus-induced inflammatory processes, or to type 1 acute myocardial infarction.[18,19] In addition, we found considerably higher levels of CRP in the COVID-19 ACS group, which might be attributed to severe myocardial cell necrosis caused by a viral infection. Remarkably, the COVID-19 ACS group had a lower left ventricular ejection fraction than the non-COVID-19 ACS group, which might imply a worse likelihood of long-term survival.[20]

We believe that the findings of our investigation would be useful in clinical practice. The presence of COVID-19 in ACS patients was significantly detrimental for one-year survival. Consequently, these patients should be closely followed-up following hospital discharge. According to our findings, we consider that these patients may also be candidates for more aggressive treatments, such as prolonged DAPT, higher dose of statin or earlier up-titration of beta blockers or renin angiotensin aldosterone system blockers. Furthermore, our analysis demonstrated a significant drop in ACS admissions during the early stages of the COVID-19 pandemic, which might have resulted in delayed treatments and increased morbidity and mortality rates. As a result, it should be remembered in future pandemics, and required precautions should be taken at the beginning of pandemics. The effect of COVID-19 on the heart in the short term might be related to elevated thrombogenicity and/or inflammation. When considering the one-year impacts of SARS-CoV-2, it is possible that additional unknown pathogenic pathways of the virus may also contribute to higher mortality, which should be investigated further in future researches

Limitations

There are some limitations about our study. First, the design of the study was a non-randomized, retrospective, single-center, and open-label. Second, the patient selection before ACS was questionable, and there might be selection bias. Third, although the power analysis of the study revealed an adequate sample size (the effect size and the power of the study were 0.143 and 94%, respectively), it included a limited number of ACS patients. Fourth, since we only assessed one-year all-cause mortality, other outcomes were not evaluated owing to the missing data. Fifth, despite the fact that a multivariable analysis was carried out, residual confounding variables might still exist. Finally, prospective studies are needed to assess cardiovascular causes of death in the follow-up of COVID-19 ACS patients.

Conclusion

Our study clearly indicated that ACS patients with COVID-19 infection at the same time had higher risk of mortality both in the short-term and the one-year periods.

Declaration of Competing Interest

All authors declare that they do not have conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This article does not contain any studies with animal subjects performed by any of the authors.

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