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par

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TITRE

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SERMENT D'HIPPOCRATE

En présence des enseignants et enseignantes
de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.
Je donnerai mes soins gratuits aux indigents,
et n'exigerai jamais un salaire au-dessus de mon travail.
Admis(e) dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.
Respectueux(euse) et reconnaissant(e) envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs parents.
Que les hommes et les femmes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert(e) d'opprobre
et méprisé(e) de mes confrères et consoeurs
si j'y manque.

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Pronostic des patients atteints d'un infarctus du myocarde concomitamment de la COVID-19 : une étude observationnelle française

RESUME

Contexte – Le pronostic des patients après un infarctus du myocarde concomitant d'une infection COVID- 19 est incertain.

Objectif – Evaluer le pronostic des patients après un infarctus du myocarde (IDM) lorsqu'ils sont infectés de manière concomitante par la COVID-19.

Méthodes – Cette étude de cohorte observationnelle rétrospective utilise le Programme de Médicalisation des Systèmes d'Information (PMSI) de la population française. Les critères de jugement sont l'incidence de la mortalité toutes causes, de la mortalité cardio-vasculaire, de la survenue d'insuffisance cardiaque, d'une récurrence d'IDM, d'un accident vasculaire cérébral ischémique, d'un épisode de fibrillation atriale, de tachycardie et/ou de fibrillation ventriculaire et d'un arrêt cardiaque.

Résultats – 288 408 patients hospitalisés pour un IDM entre le 1er mars 2020 et le 31 janvier 2023 en France ont été inclus dont 26 879 patients avaient un test COVID-19 positif dans les quinze jours précédents et jusqu'à cinq jours après admission. Les patients COVID-19 positifs étaient plus âgés, (71,4 ans vs 68,5), avaient plus souvent un antécédent d'hypertension artérielle (60,1% vs 53.9%), de diabète (27,8% vs 24,9%) d'obésité (21.6% vs 19.5%), de maladie respiratoire (16.4% vs 12.4%) dont une bronchopathie chronique obstructive (9.8% vs 7.4%) ou un syndrome d'apnée du sommeil (4.8% vs 3.8%) mais étaient moins souvent fumeurs (22,5% vs 24,1%). La présentation à l'admission était moins souvent un IDM avec sus-décalage du segment ST (49.7% vs 52.1%), et en particulier un IDM antérieur, (23.7% vs 25%) ou un IDM inférieur (16.7% vs 19%).

Après ajustement sur toutes les caractéristiques d'inclusion, les patients COVID-19 positifs présentaient une incidence supérieure de mortalité toutes causes (HR, 1.272 ; 95%CI, 1.234-1.311; p <0.0001), d'insuffisance cardiaque (HR, 1.197; 95%CI, 1.163-1.231; p <0.0001), de récurrence d'IDM (HR, 1.004 ; 95%CI, 1.009-1.081; p <0.01), d'AVC ischémique (HR, 1.205 ; 95%CI, 1.096-1.325; p <0.0001), de fibrillation atriale (HR, 1.218 ; 95%CI, 1.148-1.292 ; p <0.0001), de tachycardie et/ou fibrillation ventriculaire (HR, 1.310 ; 95%CI, 1.201-1.429; p <0.0001), d'arrêt cardiaque (HR, 1.210 ; 95%CI, 1.074-1.363 ; p <0.002). La mortalité de cause cardio-vasculaire était significativement moins élevée chez les patients COVID-19 positifs (HR, 0.946; 95%CI, 0.905-0.989 ; p = 0.02).

Un score de propension apparié sur toutes les caractéristiques d'inclusion entre deux groupes de 26 879 patients hospitalisés pour un IDM avec test COVID-19 positif d'une part et test négatif d'autre part retrouve chez les patients ayant un test positif une incidence supérieure de mortalité toutes causes (HR, 1.255 ; 95%CI, 1.203-1.308 ; p <0.0001), d'insuffisance cardiaque (HR, 1.205 ; 95%CI, 1.159-1.254 ; p <0.0001), d'AVC ischémique (HR, 1.237 ; 95%CI, 1.084-1.411; p = 0.002), de fibrillation atriale (HR, 1.160 ; 95%CI, 1.070-1.258 ; p = 0.0003),), de tachycardie et/ou fibrillation ventriculaire (1.360 ; 95%CI, 1.200-1.540 ; p <0.0001). La

mortalité de cause cardio-vasculaire était significativement moins élevée chez les patients COVID-19 positifs (HR, 0.946; 95%CI, 0.905-0.989 ; p = 0.02). On ne retrouvait pas de différence statistiquement significative pour la survenue au cours du suivi d'un arrêt cardiaque (HR, 1.156; 95%CI, 0.983-1.361 ; p = 0.08) et de récurrence d'IDM (HR, 1.013; 95%CI, 0.967-1.061 ; p = 0.60).

Conclusion – Dans cette étude rétrospective au recrutement national, la survenue d'un infarctus du myocarde avec une infection COVID-19 concomitante semble augmenter l'incidence de la mortalité toutes causes sans trouver son origine dans la mortalité cardiovasculaire.

Mots clés : infarctus du myocarde, COVID-19, mortalité toutes-causes, score de propension

Prognosis of acute myocardial infarction patients in the setting of COVID-19: A French observational study

ABSTRACT

Background – The prognosis of acute myocardial infarction (AMI) patients in the setting of COVID-19 remains uncertain.

Objective – To evaluate patients' prognosis after an AMI concomitant with COVID-19.

Methods – This retrospective observational cohort was based on the administrative hospital-discharge database from the French population. Primary outcomes were incidences of all-cause death, cardiovascular (CV) death, heart failure, recurrence of MI, ischemic stroke, incident atrial fibrillation (AF), ventricular tachycardia/ventricular fibrillation (VT/VF), and cardiac arrest.

Results – 288 408 patients hospitalized for AMI in France from March 1st, 2020, to January 31st, 2023, were included; 26 879 had a COVID-19-positive test between 15 days prior to admission up to 5 days after. COVID-19-positive patients were older (71,4 vs 68,5), had more frequently diabetes mellitus (27,8% vs 24,9%) and a higher obesity rate (21.6% vs 19.5%) but were less frequently smokers (22,5% vs 24,1%). At baseline, COVID-19-positive patients had less STEMI presentation (49.7% vs 52.1%) and more frequently lung disease (16.4% v 12.4%) including chronic obstructive pulmonary disease (9.8% v 7.4%) and sleep apnoea syndrome (4.8% vs 3.8%).

After adjustment for all patients' baseline characteristics, COVID-19 positive patients had a higher incidence of all-cause death (HR, 1.272 ; 95%CI, 1.234-1.311; p <0.0001), heart failure (HR, 1.197; 95%CI, 1.163-1.231; p <0.0001), recurrence of MI (HR, 1.004 ; 95%CI, 1.009-1.081; p <0.01), ischemic stroke (HR, 1.205 ; 95%CI, 1.096-1.325; p <0.0001), incident AF (HR, 1.218 ; 95%CI, 1.148-1.292 ; p <0.0001), VT/VF (HR, 1.310 ; 95%CI, 1.201-1.429; p <0.0001), cardiac arrest (HR, 1.210 ; 95%CI, 1.074-1.363 ; p <0.002). Cardiovascular death incidence was significantly lower in COVID-19 positive patients (HR, 0.946; 95%CI, 0.905-0.989; p = 0.02).

Propensity score matching analysis included 26 879 COVID-19 patients versus 26 879 patients without COVID-19 in this AMI population. The two groups were matched for all-baseline characteristics. COVID-19 patients had a higher incidence of all-cause death (HR, 1.255; 95%CI, 1.203-1.308; p <0.0001), heart failure (HR, 1.205; 95%CI, 1.159-1.254; p <0.0001), ischemic stroke (HR, 1.237; 95%CI, 1.084-1.411; p = 0.002), incident AF (HR, 1.160; 95%CI, 1.070-1.258; p = 0.0003), VT/VF (1.360; 95%CI, 1.200-1.540; p <0.0001). Cardiovascular death incidence was lower in COVID-19 patients (HR, 0.932; 95%CI, 0.879-0.988; p = 0.02). No statistical difference was found for cardiac arrest incidence (HR, 1.156; 95%CI, 0.983-1.361; p = 0.08) or recurrence of MI (HR, 1.013; 95%CI, 0.967-1.061; p = 0.6).

Conclusion – In this large French nationwide cohort study, occurrence of AMI when being infected with SARS-Cov2 increases all-cause death incidence, yet this decreased prognosis is not due to cardiovascular death. Further investigations are needed to elucidate aetiologies of death in this population.

Keys words: acute myocardial infarction, COVID-19, mortality, propensity score matching

Abbreviations

AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
HF	Heart Failure
HR	Hazard Ratio
ICD	Implantable Cardioverter-Defibrillator
ICD-10	The 10th revision of the International Classification of Diseases
IQR	Interquartile Range
MI	Myocardial Infarction
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
SDs	Standard Deviations
STEMI	ST-segment Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PMSI	Programme de Médicalisation des Systèmes d'Information
VF	Ventricular fibrillation
VT	Ventricular tachycardia
TTS	Tako Tsubo Syndrome
y.o.	Years old

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1. Introduction

Acute myocardial infarction (AMI) is a frequent and severe disease responsible for more than a third of deaths in developed nations annually[1–4]. It occurs in 80 000 patients every year with 15 000 deaths in France[5,6].

Its prognosis significantly improved in the last decades due to the development of new medications, advances in interventional techniques, and the spread of cardiac rehabilitation [5,7–9]. These improvements were challenged by the coronavirus disease of 2019 (COVID-19) pandemic mainly because of saturated health-care system emergencies.

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) declared this disease as a "public health emergency of international concern" on January 30, 2020[10]. It resulted in considerable mortality with 7 million deaths worldwide as of 30th May 2023[11]. COVID-19 induces an overproduction of inflammatory cytokines (IL-6 and TNF-α) leading to systemic inflammation and multiple organ dysfunction syndrome[12], thus worsening prognosis of patients especially when they present acute respiratory distress syndrome (ARDS)[13,14] and myocardial injury[15,16],

However, data about AMI and concurrent COVID-19 are contradictory. Recent studies showed that COVID-19 patients admitted for AMI have higher thrombus burden[17–19], rate of cardiac arrest on admission[19], incidence of no-reflow[19], in-hospital mortality[17–21] and stent thrombosis[21].These poor outcomes seem not to be related with COVID-19 symptoms but to the viral load of SARS-CoV-2 with two additional effects : (1) higher inflammatory response and (2) direct SARS-CoV-2 effect with an active pro-thrombotic role[22]. Conversely, Grave et al. didn't found any prognosis difference at 3 months after AMI during COVID-19 crisis in the French population[23].

The aim of our study was to evaluate the prognosis of AMI patients when infected with SARS-CoV-2.

2. Methods

2.1. Study design and participants

This retrospective observational cohort study was performed using the National Hospital Discharge Database (Programme de Médicalisation des Systèmes d'Information, PMSI), which collects all data on admission in the 2 989 French healthcare facilities[24] (public and private hospitals). Data about the main diagnosis for hospital stay, patients' characteristics and hospital deaths are available and used since 2004 for reimbursement and fee-for-service pricing of the hospitals. PMSI is a part of the French National Health Data System (Système National des Données de Santé [SNDS]), which contains also socio-economic information, demographic data and the date of death of all individuals.

Between 1st March 2020 and 31st January 2023, all patients aged 18 years old and more hospitalized for AMI in France were included. We used the International Classification of Diseases, Tenth Revision (ICD-10) to select AMI patients (defined by codes I21 to I23). We chose to exclude patients who had ARDS during their hospitalisation. The reason for excluding these patients were dual: first, AMI was generally not the main diagnosis and cause for hospitalization and, if coded, may generally only correspond to an isolated elevation of cardiac biomarkers, independently of the coronary status of the patients, second because ARDS is associated with an independent bad prognosis[13,14]. We defined COVID-19 patients as patients having a positive COVID-19 test (antigenic or PCR) from 15 days before up to 5 days after admission for AMI, considering that this interval included the incubation period when patients are contagious as well as the period when systemic inflammation is at its highest with production of inflammatory cytokines[12] and seroconversion occurring between 7 and 14 days after the onset of symptoms[25,26]. Recent meta-analysis over 141 studies found that the pooled incubation period was 6,57 days and ranged from 1.80 to 18.87 days[27].

2.2. Outcomes

Primary outcomes were incidences of all-cause death, cardiovascular (CV) death, heart failure, recurrence of MI, ischemic stroke, incident atrial fibrillation (AF), ventricular tachycardia/ventricular fibrillation (VT/VF), and cardiac arrest.

2.3. Statistical analysis

Qualitative variables are described as frequencies and percentages and quantitative variables as means (±standard deviations [SDs]). Comparisons were made using chi-square tests for categorical variables and Student's t-test or the non-parametric Kruskal−Wallis test, as appropriate, for continuous variables.

Owing to the non-randomized nature of the study and considering the differences in baseline characteristics between AMI patients with concurrent COVID-19 or without COVID-19 (controls), propensity-score matching was used to control for potential confounders of the treatment−outcome relationship. Propensity score was calculated using logistic regression with COVID-19 as the dependent variable. The propensity score included the baseline characteristics listed in table 1. For each patient with COVID-19, a propensity-score matched patient without COVID-19 was selected (1:1) using the one-to-one nearest neighbour method (with a calliper of 0.001 of the SD of the propensity score on the logit scale) and no replacement.

We assessed the distributions of demographic data and comorbidities in the COVID-19 group and control cohorts with standardized differences, which were calculated as the difference in the means or proportions of a variable divided by a pooled estimate of the SD of that variable. A standardized difference of ≤5% indicated a negligible difference between the means of the two cohorts. For the outcomes analysis in the matched cohort, the incidence rates (%/y) for each outcome of interest during follow-up were estimated in the COVID-19 group and control cohorts and were compared using incidence rate ratios. Hazard ratios (HRs) were calculated from Cox regression. We used Cox proportional hazard regression models with attained person-time to determine hazard ratios (HRs) and corresponding 95% CIs for the associations between COVID-19 and risk of death, including all-cause and CV death respectively in AMI patients. Variables incorporated into the multivariable model included all patients baseline characteristics.

Regarding the characteristic of the clinical outcomes and its non-specific relation to COVID status, we also performed further sub-group analyses of the occurrence of the primary composite outcome according to patient characteristics. In the sub-group analyses, the clinical outcomes and covariates used were the same as those in the main propensity-score matching analysis. All comparisons with $p<0.05$ were considered statistically significant. All analyses were performed using Enterprise Guide 7.1 (SAS Institute Inc).

2.4. Patient consent—ethics approval

The study was conducted retrospectively. As patients were not involved in its conduct, there was no effect on their care. All data were anonymized and ethical approval was not therefore required. Procedures for data collection and management were approved by the Commission Nationale de l'Informatique et des Libertés, the independent National Ethical Committee protecting human rights in France, which ensures that all information is kept confidential and anonymous (authorization number 1897139).

3. RESULTS

From 1st March 2020 to 31st January 2023, 288 408 patients were hospitalized for AMI in France, of whom 26 879 had a COVID-19 positive test (Figure 1).

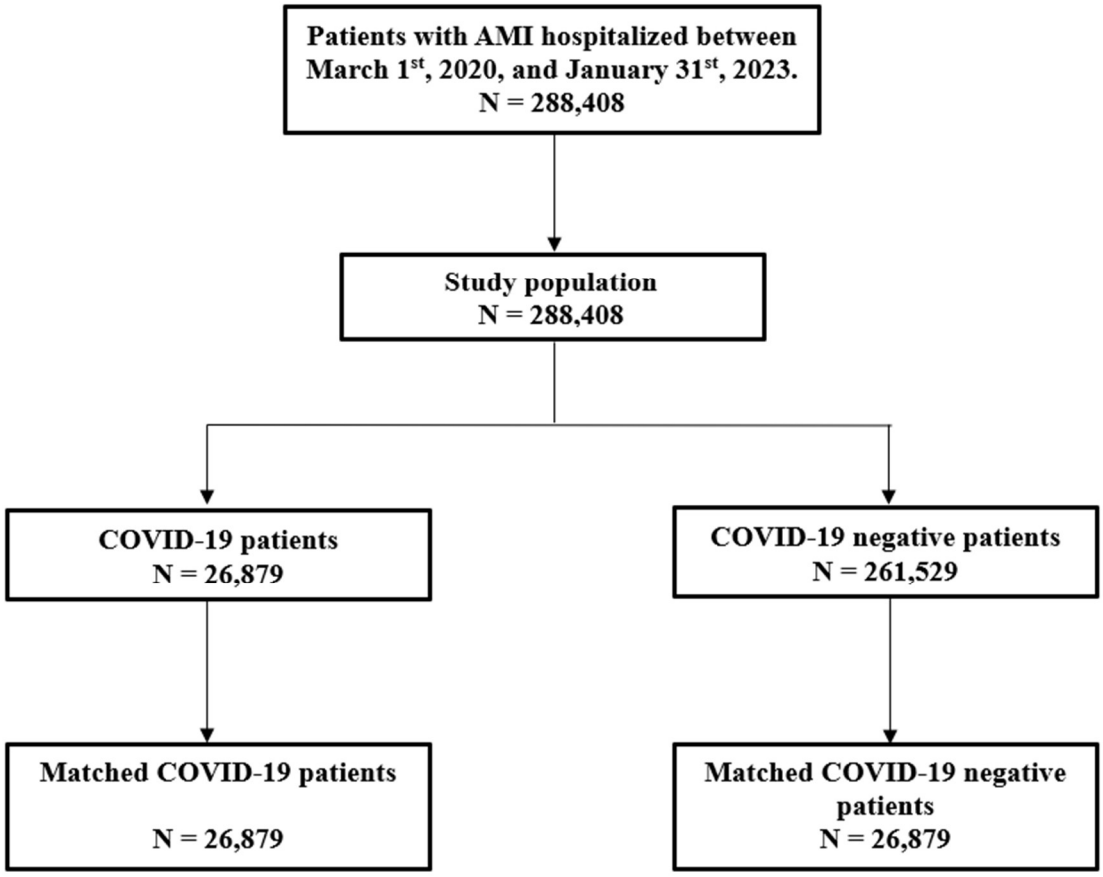


Figure 1. Flow chart.

Abbreviations Figure 1: AMI: Acute Myocardial Infarction, COVID-19: Coronavirus Disease 2019.

3.1. Baseline characteristics of the study population

COVID-19 positive patients were older (71,4 y.o. vs 68,5; Table 1), had more frequently arterial hypertension (60,1% vs 53.9%), diabetes mellitus (27,8% vs 24,9%) and obesity defined as a body mass index > 30 kg/m² (21.6% vs 19.5%) but were less frequently active smokers (22,5% vs 24,1%). At baseline, COVID-19 positive patients had more acute heart failure (32,6% vs 26,3%), including pulmonary oedema and cardiogenic shock (5,7% vs 4,4%) at presentation, poorer nutritional status (17,7% vs 10,7%), more anaemia (17,5% vs 13,1%), history of pulmonary oedema (6,6% vs 5%), history of valve disease (14,8% vs 11,7%), non

ST-segment elevation myocardial infarction (NSTEMI) presentation (50,3% vs 47.9%), history of peripheral vascular disease (13% vs 11,9%), history of atrial fibrillation (22,9% vs 17,3%), history of dilated cardiomyopathy (6,3% vs 4,8%), previous pacemaker or ICD (4,9% vs 4,1%), history of ischemic stroke (5,3% vs 4,1%), history of intracranial bleeding (1,9% vs 1,4%), previous cancer (13,4% vs 12%) including metastatic cancer (2,6% vs 2,3%), history of chronic kidney disease (10,2% vs 7,7%), history of lung disease (16.4% vs 12.4%) including chronic obstructive pulmonary disease (COPD) (9.8% vs 7.4%) and sleep apnoea syndrome (4.8% vs 3.8%), history of liver disease (4,8% vs 3,8%). COVID-19 positive patients had also less frequently anterior (23.7% vs 25%) and inferior AMI presentation (16.7% vs 19%), STEMI (49.7% vs 52.1%). The percentage of illicit drug use (1%), previous MI (0,1%), previous CABG (2,6%), dialysis (1,9% vs 1,7%) were comparable in the two groups.

3.2. Outcomes

3.2.1. Adjusted analysis

After adjustment for all patients' baseline characteristics (Table 1), COVID-19 patients had a higher incidence of all-cause death (36.47%/year vs 15.9%; adjusted HR, 1.272 ; 95%CI, 1.234-1.311; p <0.0001; Table 2), heart failure (50,79%/year vs 26.97%; adjusted HR, 1.197; 95%CI, 1.163-1.231; p <0.0001), recurrence of MI (31.3%/year vs 26.39%; adjusted HR, 1.004 ; 95%CI, 1.009-1.081; p <0.01), ischemic stroke (3.65%/year vs 2.22%; adjusted HR, 1.205 ; 95%CI, 1.096-1.325; p <0.0001), incident AF (13%/year vs 7.79%; adjusted HR, 1.218 ; 95%CI, 1.148-1.292 ; p <0.0001), VT/VF (4.83%/year vs 3.10%; adjusted HR, 1.310 ; 95%CI, 1.201-1.429; p <0.0001), cardiac arrest (2.36%/year vs 1.56 %; adjusted HR, 1.210 ; 95%CI, 1.074-1.363 ; p <0.002). COVID-19 patients had a lower incidence of CV death (15.97%/year vs 9.29%; adjusted HR, 0.946; 95%CI, 0.905-0.989; p = 0.02).

Table 1. Baseline medical characteristics observed in AMI patients with COVID-19 compared to AMI patients without Covid-19.

	No Covid-19 (n=261 529)	Covid-19 (n=26 879)	p	Total (n=288 408)
Age (years), mean ± SD	68.5±14.3	71.4±14.7	<0.0001	68.8±14.3
Male gender, n (%)	177029 (67.7)	17238 (64.1)	<0.0001	194266 (67.4)
Arterial hypertension, n (%)	140860 (53.9)	16154 (60.1)	<0.0001	157014 (54.4)
Diabetes mellitus, n (%)	65095 (24.9)	7480 (27.8)	<0.0001	72575 (25.2)
Dyslipidaemia, n (%)	82120 (31.4)	8558 (31.8)	0.13	90678 (31.4)
Active smoker, n (%)	63133 (24.1)	6050 (22.5)	<0.0001	69184 (24.0)
Obesity, n (%)	50894 (19.5)	5814 (21.6)	<0.0001	56707 (19.7)
HF at the acute phase, n (%)	68861 (26.3)	8752 (32.6)	<0.0001	77612 (26.9)
Pulmonary oedema / cardiogenic shock at the acute phase, n (%)	11455 (4.4)	1540 (5.7)	<0.0001	12995 (4.5)
Anterior MI, n (%)	65435 (25.0)	6368 (23.7)	<0.0001	71802 (24.9)
Inferior MI, n (%)	49795 (19.0)	4489 (16.7)	<0.0001	54284 (18.8)
MI with other location, n (%)	146299 (55.9)	16023 (59.6)	<0.0001	162322 (56.3)
STEMI, n (%)	136335 (52.1)	13367 (49.7)	<0.0001	149702 (51.9)
NSTEMI, n (%)	125194 (47.9)	13512 (50.3)	<0.0001	138706 (48.1)
Poor nutritional status, n (%)	28088 (10.7)	4760 (17.7)	<0.0001	32848 (11.4)
Anaemia, n (%)	34365 (13.1)	4707 (17.5)	<0.0001	39071 (13.5)
Illicit drug use, n (%)	2981 (1.1)	274 (1.0)	0.08	3256 (1.1)
History of pulmonary oedema, n (%)	13155 (5.0)	1761 (6.6)	<0.0001	14915 (5.2)
Valvular disease, n (%)	30468 (11.7)	3975 (14.8)	<0.0001	34444 (11.9)
Previous MI, n (%)	272 (0.1)	27 (0.1)	0.86	299 (0.1)
Previous PCI, n (%)	12920 (4.9)	1204 (4.5)	0.001	14124 (4.9)
Previous CABG, n (%)	6669 (2.6)	693 (2.6)	0.76	7362 (2.6)
Vascular disease, n (%)	31174 (11.9)	3505 (13.0)	<0.0001	34679 (12.0)
Atrial fibrillation, n (%)	45349 (17.3)	6142 (22.9)	<0.0001	51491 (17.9)
Dilated cardiomyopathy, n (%)	12606 (4.8)	1693 (6.3)	<0.0001	14299 (5.0)
Previous pacemaker or ICD, n (%)	10749 (4.1)	1328 (4.9)	<0.0001	12077 (4.2)
Ischemic stroke, n (%)	10644 (4.1)	1419 (5.3)	<0.0001	12063 (4.2)
Intracranial bleeding, n (%)	3609 (1.4)	519 (1.9)	<0.0001	4128 (1.4)
Previous cancer, n (%)	31253 (12.0)	3594 (13.4)	<0.0001	34846 (12.1)
Metastatic cancer, n (%)	5963 (2.3)	702 (2.6)	0.001	6664 (2.3)
Chronic kidney disease, n (%)	20164 (7.7)	2736 (10.2)	<0.0001	22900 (7.9)
Dialysis, n (%)	4420 (1.7)	508 (1.9)	0.02	4928 (1.7)
Lung disease, n (%)	32299 (12.4)	4405 (16.4)	<0.0001	36704 (12.7)
COPD, n (%)	19327 (7.4)	2626 (9.8)	<0.0001	21953 (7.6)
Sleep apnoea syndrome, n (%)	18176 (7.0)	1992 (7.4)	0.005	20168 (7.0)
Liver disease, n (%)	9938 (3.8)	1285 (4.8)	<0.0001	11223 (3.9)

Abbreviations Table 1: CABG: Coronary Artery Bypass Graft, COPD: Chronic Obstructive Pulmonary Disease, COVID-19: Coronavirus Disease 2019, HF: Heart Failure, ICD: Implantable Cardioverter-Defibrillator, MI: Myocardial Infarction, n: number, NSTEMI: Non-ST Elevation Myocardial Infarction, PCI: Percutaneous Coronary Intervention, SD: Standard Deviations, STEMI: ST Elevation Myocardial Infarction.

Table 2. Incident outcomes in the population according to COVID-19 status.

	No Covid-19 (n=261 529)			Covid-19 (n=26 879)						
	Person-time (patient.year)	**Number of events**	**Incidence, %/year (95% CI)**	**Person-time (patient.year)**	**Number of events**	**Incidence, %/year (95% CI)**	**Incidence rate ratio (95% CI)**	**p value**	**Adjusted hazard ratio (95% CI)**	**p value**
All-cause death	203602	32372	15.90 (15.73-16.07)	13656	4981	36.47 (35.46-37.49)	2.294 (2.227-2.363)	<0.0001	1.272 (1.234-1.311)	<0.0001
Cardiovascular death	203602	18904	9.29 (9.15-9.42)	13656	2181	15.97 (15.30-16.64)	1.720 (1.646-1.798)	<0.0001	0.946 (0.905-0.989)	0.02
Heart failure	166495	44902	26.97 (26.72-27.22)	10695	5432	50.79 (49.44-52.14)	1.883 (1.831-1.937)	<0.0001	1.197 (1.163-1.231)	<0.0001
Recurrence of MI	164461	43399	26.39 (26.14-26.64)	11502	3600	31.30 (30.28-32.32)	1.186 (1.146-1.227)	<0.0001	1.044 (1.009-1.081)	0.01
Ischemic stroke	200244	4440	2.22 (2.15-2.28)	13489	492	3.65 (3.33-3.97)	1.645 (1.499-1.806)	<0.0001	1.205 (1.096-1.325)	0.0001
Incident AF	160006	12458	7.79 (7.65-7.92)	9661	1256	13.00 (12.28-13.72)	1.670 (1.576-1.770)	<0.0001	1.218 (1.148-1.292)	<0.0001
VT/VF	184053	5708	3.10 (3.02-3.18)	12101	584	4.83 (4.44-5.22)	1.556 (1.429-1.694)	<0.0001	1.310 (1.201-1.429)	<0.0001
Cardiac arrest	198449	3096	1.56 (1.51-1.62)	13211	312	2.36 (2.10-2.62)	1.514 (1.347-1.701)	<0.0001	1.210 (1.074-1.363)	0.002

Abbreviations Table 2: CI: Confidence Interval, COVID-19: Coronavirus Disease 2019, HF: Heart Failure, MI: Myocardial Infarction, n: number, VF: Ventricular Fibrillation, VT: Ventricular Tachycardia.

3.2.2. Propensity-score matching analysis

Propensity-score matching analysis included 53 758 patients (Figure 1) with 26 879 COVID-19 patients and 26 879 COVID-19 negative patients, The two groups were matched for all baseline characteristics (Table 3). COVID-19 patients had a higher incidence of all-cause death (36.74%/year vs 25.90%; adjusted HR, 1.255 ; 95%CI, 1.203-1.308 ; p <0.0001; Table 4), heart failure (50.23%/year vs 38.12%; adjusted HR, 1.205 ; 95%CI, 1.159-1.254 ; p <0.0001), ischemic stroke (3.65%/year vs 2.74%; adjusted HR, 1.237 ; 95%CI, 1.084-1.411; p= 0.002), incident AF (9.63%/year vs 7.91%; adjusted HR, 1.160 ; 95%CI, 1.070-1.258 ; p = 0.0003), VT/VF (4.36%/year vs 3.03%; adjusted HR, 1.360 ; 95%CI, 1.200-1.540 ; p <0.0001). COVID-19 patients had a lower incidence of CV death (15.06%/year vs 15.97%; adjusted HR, 0.932; 95%CI, 0.879-0.988; p = 0.02).

There was no statistical difference in the incidence of cardiac arrest (2.29%/year vs 1.95 %; adjusted HR, 1.156; 95%CI, 0.983-1.361; p = 0.08) and recurrence of MI (30.99%/year vs 29.57%; adjusted HR, 1.013; 95%CI, 0.967-1.061; p = 0.60).

Table 3. Baseline medical diagnoses observed in patients with Covid-19 compared to unmatched and matched controls with no Covid-19.

	Before PS matching			After PS matching		
	No Covid-19 (n=261529)	**Covid-19 (n=26879)**	**Standardized difference (%)**	**No Covid-19 (n=26879)**	**Covid-19 (n=26879)**	**Standardized difference (%)**
Age (years), mean ± SD	68.5±14.3	71.4±14.7	20.5	71.4±14.1	71.4±14.7	-0.1
Male gender, n (%)	177029 (67.7)	17238 (64.1)	-7.6	17218 (64.1)	17237 (64.1)	0.1
Arterial hypertension, n (%)	140860 (53.9)	16154 (60.1)	12.5	16097 (59.9)	16154 (60.1)	0.4
Diabetes mellitus, n (%)	65095 (24.9)	7480 (27.8)	6.8	7373 (27.4)	7480 (27.8)	0.9
Dyslipidaemia, n (%)	82120 (31.4)	8558 (31.8)	0.9	8432 (31.4)	8558 (31.8)	1.0
Active smoker, n (%)	63133 (24.1)	6050 (22.5)	-3.8	6131 (22.8)	6050 (22.5)	-0.7
Obesity, n (%)	50894 (19.5)	5814 (21.6)	5.5	5824 (21.7)	5814 (21.6)	-0.1
HF at the acute phase, n (%)	68861 (26.3)	8752 (32.6)	14.1	8671 (32.3)	8751 (32.6)	0.6
Pulmonary oedema / cardiogenic shock at the acute phase, n (%)	11455 (4.4)	1540 (5.7)	6.5	1556 (5.8)	1540 (5.7)	-0.3
Anterior MI, n (%)	65435 (25.0)	6368 (23.7)	-3.1	6319 (23.5)	6367 (23.7)	0.4
Inferior MI, n (%)	49795 (19.0)	4489 (16.7)	-6.0	4472 (16.6)	4491 (16.7)	0.2
MI with other location, n (%)	146299 (55.9)	16023 (59.6)	7.4	16086 (59.9)	16022 (59.6)	-0.5
STEMI, n (%)	136335 (52.1)	13367 (49.7)	-4.8	13326 (49.6)	13369 (49.7)	0.3
NSTEMI, n (%)	125194 (47.9)	13512 (50.3)	4.8	13552 (50.4)	13509 (50.3)	-0.3
Poor nutritional status, n (%)	28088 (10.7)	4760 (17.7)	22.0	4626 (17.2)	4760 (17.7)	1.3
Anaemia, n (%)	34365 (13.1)	4707 (17.5)	12.8	4454 (16.6)	4706 (17.5)	2.5
Illicit drug use, n (%)	2981 (1.1)	274 (1.0)	-1.1	268 (1.0)	274 (1.0)	0.2
History of pulmonary oedema, n (%)	13155 (5.0)	1761 (6.6)	6.9	1755 (6.5)	1761 (6.6)	0.1
Valvular disease, n (%)	30468 (11.7)	3975 (14.8)	9.7	3919 (14.6)	3975 (14.8)	0.6
Previous MI, n (%)	272 (0.1)	27 (0.1)	-0.1	16 (0.1)	27 (0.1)	1.4
Previous PCI, n (%)	12920 (4.9)	1204 (4.5)	-2.1	1072 (4.0)	1204 (4.5)	2.4
Previous CABG, n (%)	6669 (2.6)	693 (2.6)	0.2	683 (2.5)	693 (2.6)	0.3
Vascular disease, n (%)	31174 (11.9)	3505 (13.0)	3.4	3180 (11.8)	3505 (13.0)	3.7
Atrial fibrillation, n (%)	45349 (17.3)	6142 (22.9)	14.4	5967 (22.2)	6142 (22.9)	1.6
Dilated cardiomyopathy, n (%)	12606 (4.8)	1693 (6.3)	6.8	1602 (6.0)	1693 (6.3)	1.4
Previous pacemaker or ICD, n (%)	10749 (4.1)	1328 (4.9)	4.1	1285 (4.8)	1328 (4.9)	0.7
Ischemic stroke, n (%)	10644 (4.1)	1419 (5.3)	6.0	1363 (5.1)	1416 (5.3)	0.9
Intracranial bleeding, n (%)	3609 (1.4)	519 (1.9)	4.6	500 (1.9)	516 (1.9)	0.4
Previous cancer, n (%)	31253 (12.0)	3594 (13.4)	4.4	3419 (12.7)	3596 (13.4)	2.0
Metastatic cancer, n (%)	5963 (2.3)	702 (2.6)	2.2	656 (2.4)	702 (2.6)	1.1
Chronic kidney disease, n (%)	20164 (7.7)	2736 (10.2)	9.1	2564 (9.5)	2736 (10.2)	2.1
Dialysis, n (%)	4420 (1.7)	508 (1.9)	1.5	419 (1.6)	508 (1.9)	2.5
Lung disease, n (%)	32299 (12.4)	4405 (16.4)	12.1	4263 (15.9)	4405 (16.4)	1.4
COPD, n (%)	19327 (7.4)	2626 (9.8)	9.0	2494 (9.3)	2623 (9.8)	1.6
Sleep apnoea syndrome, n (%)	18176 (7.0)	1992 (7.4)	1.8	1967 (7.3)	1992 (7.4)	0.3
Liver disease, n (%)	9938 (3.8)	1285 (4.8)	5.1	1234 (4.6)	1285 (4.8)	0.9

Abbreviations Table 3: CABG: Coronary Artery Bypass Graft, COPD: Chronic Obstructive Pulmonary Disease, COVID-19: Coronavirus Disease 2019, HF: Heart Failure, ICD: Implantable cardioverter-defibrillator, MI: Myocardial Infarction, n: number, NSTEMI: Non-ST Elevation Myocardial Infarction, PCI: Percutaneous Coronary Intervention, PS: Propensity Score, SD: Standard Deviations, STEMI: ST Elevation Myocardial Infarction.

Table 4. Incident outcomes in the matched population according to COVID-19 status.

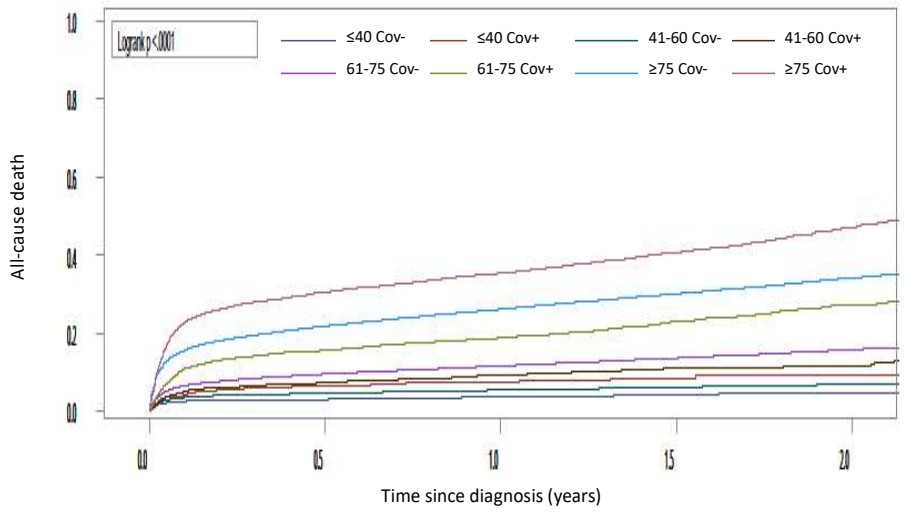
	No COVID-19 (n=26879)			COVID-19 (n=26879)						
	Person-time (patient.year)	**Number of events**	**Incidence, %/year (95% CI)**	**Person-time (patient.year)**	**Number of events**	**Incidence, %/year (95% CI)**	**Incidence rate ratio (95% CI)**	**p value**	**Hazard ratio (95% CI)**	**p value**
All-cause death	15644	4051	25.90 (25.10-26.69)	13656	4981	36.47 (35.46-37.49)	1.408 (1.351-1.468)	<0.0001	1.255 (1.203-1.308)	<0.0001
Cardiovascular death	15644	2356	15.06 (14.45-15.67)	13656	2181	15.97 (15.30-16.64)	1.060 (1.000-1.124)	0.05	0.932 (0.879-0.988)	0.02
Heart failure	12559	4788	38.12 (37.05-39.20)	10815	5432	50.23 (48.89-51.56)	1.317 (1.267-1.370)	<0.0001	1.205 (1.159-1.254)	<0.0001
Recurrence of MI	13079	3867	29.57 (28.64-30.50)	11615	3600	30.99 (29.98-32.01)	1.048 (1.002-1.097)	0.04	1.013 (0.967-1.061)	0.60
Ischemic stroke	15421	422	2.74 (2.48-3.00)	13489	492	3.65 (3.33-3.97)	1.333 (1.170-1.518)	<0.0001	1.237 (1.084-1.411)	0.002
Incident AF	14839	1174	7.91 (7.46-8.36)	13045	1256	9.63 (9.10-10.16)	1.217 (1.124-1.318)	<0.0001	1.160 (1.070-1.258)	0.0003
VT/VF	15370	465	3.03 (2.75-3.30)	13389	584	4.36 (4.01-4.72)	1.442 (1.276-1.628)	<0.0001	1.360 (1.200-1.540)	<0.0001
Cardiac arrest	15608	304	1.95 (1.73-2.17)	13613	312	2.29 (2.04-2.55)	1.177 (1.005-1.378)	0.04	1.156 (0.983-1.361)	0.08

Abbreviations Table 4: CI: Confidence Interval, COVID-19: Coronavirus Disease 2019, HF: Heart Failure, MI: Myocardial Infarction, VF: Ventricular Fibrillation, VT: Ventricular tachycardia.

3.2.3. COVID-19 mortality according to specific characteristics

As expected, the mortality rates of COVID-19 patients increased with age after AMI (Figure 2). Unsurprisingly, COVID-19 patients aged ≥75 y.o. had the worst prognosis with almost 40% mortality rate after 2 years of follow-up. Patients aged ≥75 y.o. without COVID infection had an increased incidence of all cause-death compared to younger patients without taking into account COVID-19 status.

Patients with higher mortality rates >20% at 2 years of follow up were COVID-19 patients aged 60-74 y.o. and ≥75 y.o. and COVID-19 negative patients aged > 75 y.o.



Nb at risk

≤40 yo, Covid -	12833	4143	2969	2198	1628
≤40 yo, Covid +	1104	313	208	115	40
41-60 yo, Covid -	60551	19283	13729	9515	6635
41-60 yo, Covid +	4866	1477	938	545	230
61-75 yo, Covid -	93883	34437	24153	15992	10379
61-75 yo, Covid +	8811	3223	2149	1253	525
≥75 yo, Covid -	94162	33435	22697	14841	9479
≥75 yo, Covid +	12098	3955	2556	1500	561

Figure 2. Mortality according to age and COVID status in AMI population.

Abbreviations Figure 2: COVID: Coronavirus Disease 2019, Cov: Coronavirus disease 2019, Covid +: COVID-19 patients, Covid -: COVID-19 negative patients, Nb: number, yo: years old.

Being infected with SARS-Cov2 during AMI increases incidence of all-cause death but this is not related to AMI presentation, i.e., STEMI versus NSTEMI. As we can see in Figure 3, mortality rates of COVID-19 patients approximate 35% after 2 years of follow-up with STEMI and NSTEMI curves meeting up. The same observation can be made for patients not infected with SARS-Cov2 with an all-cause mortality rate near 20% at 2 years of follow-up.

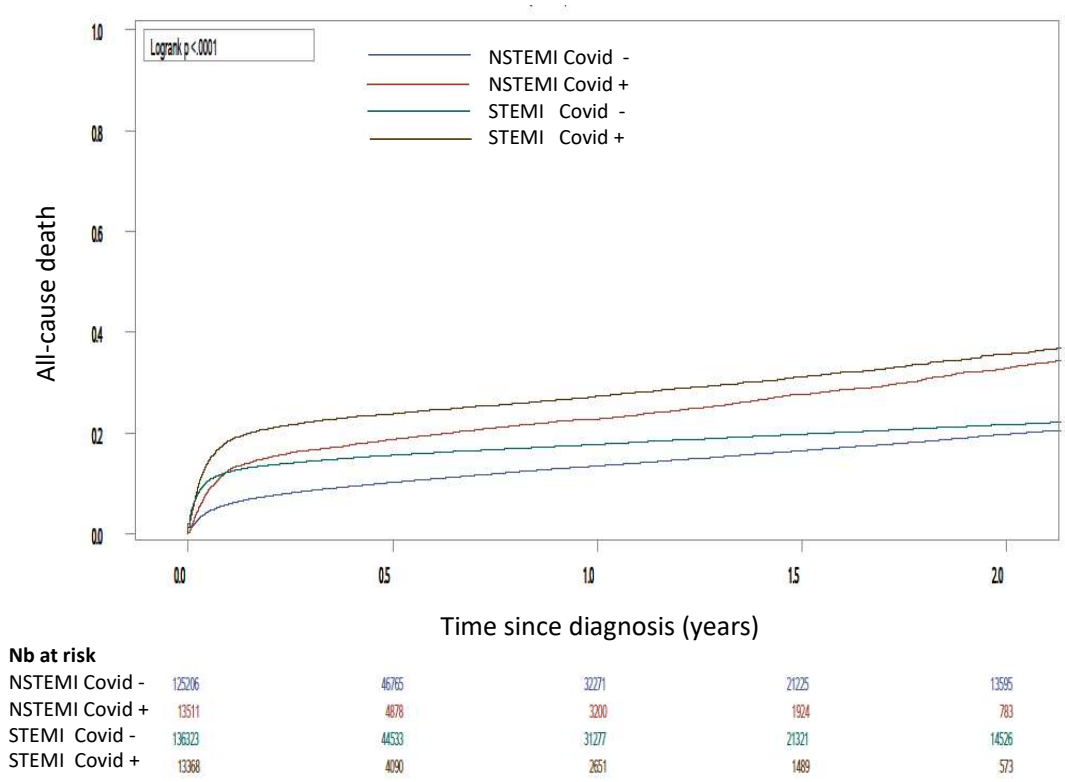


Figure 3. Mortality rate according to COVID-19 status and STEMI versus NSTEMI diagnosis.

Abbreviations Figure 3: COVID: Coronavirus Disease 2019; Covid +: COVID-19 positive test, Covid -: COVID-19 negative test, NSTEMI: Non-ST Elevation Myocardial Infarction, Nb: number, STEMI: ST Elevation Myocardial Infarction.

3.2.4. Prevalence of AMI according to time and COVID-19 Status

We know that patients' frequency of visits to hospitals changed with COVID-19 pandemic and successive lockdowns, and we can observe this variation in the number of hospitalisations for AMI according to month of admission in figure 4. In fact, we can see that there were more patients with AMI with or without concurrent COVID-19 hospitalized in April and May 2020 compared to March 2020 when the lockdown began in France, in a time when patients had a huge fear of being infected or hospitalized. Similar peaks of hospitalisations are seen in November 2020 (second French lockdown), in April and May 2021 (third French lockdown), in November and December 2021 (fifth COVID-19 wave with DELTA and OMICRON variants).

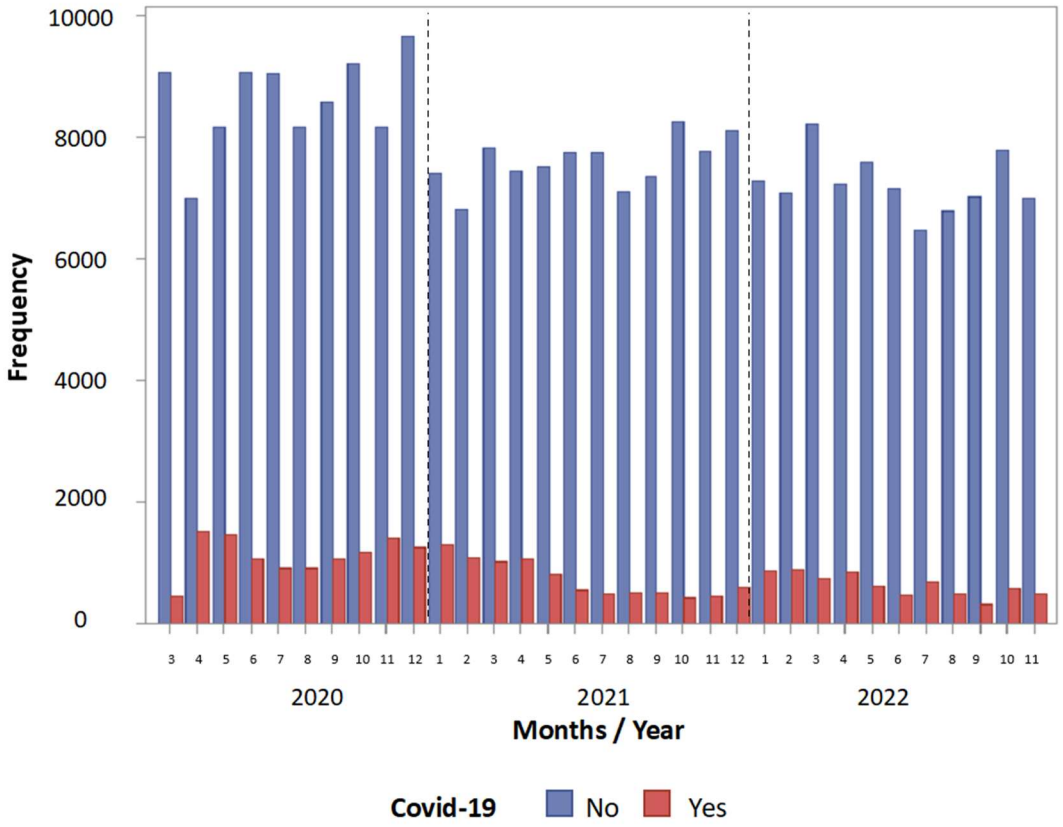


Figure 4. Number of patients admitted for AMI per month according to the month of admission and COVID-19 status.

Abbreviations Figure 4: AMI: Acute Myocardial Infarction

3.2.5. Subgroup interaction analyses

Subgroup interaction analyses (Table 5.) showed us that incidence of all-cause death significantly increased in male patients (adjusted HR for interaction, 1.239; 95%CI, 1.166-1.316; p <0.0001), patients with obesity (adjusted HR for interaction, 1.108; 95%CI, 1.029-1.192; p = 0.006) and patients with dyslipidemia (adjusted HR for interaction, 1.067; 95%CI, 1.001-1.138; p = 0.045), after adjustment for all others baselines characteristics.

There was no significant difference for diabetes mellitus (adjusted HR for interaction, 0.994; 95%CI, 0.934-1.058; p = 0.85); active smoking status (adjusted HR for interaction, 1.021; 95%CI, 0.941 -1.109; p = 0.61) and sleep apnoea syndrome (adjusted HR for interaction, 1.094; 95%CI, 0.953 -0.953; p = 0.10).

Three factors appeared inversely associated with all-cause death (Figure 5.): age $\geq$ 70 y.o. (adjusted HR for interaction, 0.896; 95%CI, 0.831-0.967; p = 0.005), arterial hypertension (adjusted HR for interaction, 0.912; 95%CI, 0.854-0.974; p = 0.006) and previous cancer (adjusted HR for interaction, 0.888; 95%CI, 0.828 -0.953; P = 0.001).

Table 5. Sub-group analyses and interaction of risk-factors with COVID-19 for the outcome of all-cause death.

	No COVID-19 (n=261529)		COVID-19 (n=26879)							
	Number of patients	Number of events	Number of patients	Number of events	Hazard ratio (95% CI)	p value	Hazard ratio for interaction	p value for interaction	Adjusted HR for interaction	p value for interaction
Age <70 years old	133254	7583	11362	926	1.622 (1.515-1.738)	<0.0001				
Age ≥70 years old	128275	24789	15517	4055	1.501 (1.451-1.552)	<0.0001	0.910 (0.844-0.982)	0.02	0.896 (0.831-0.967)	0.005
Gender (female)	84509	13109	9641	2009	1.431 (1.365-1.500)	<0.0001				
Gender (male)	177020	19263	17238	2972	1.794 (1.725-1.865)	<0.0001	1.249 (1.176-1.328)	<0.0001	1.239 (1.166-1.316)	<0.0001
No Arterial Hypertension	120682	10520	10725	1429	1.640 (1.552-1.734)	<0.0001				
Arterial Hypertension	140847	21852	16154	3552	1.613 (1.556-1.671)	<0.0001	0.936 (0.876-0.999)	0.05	0.912 (0.854-0.974)	0.006
No Diabetes mellitus	196436	21182	19399	3203	1.655 (1.594-1.718)	<0.0001				
Diabetes mellitus	65093	11190	7480	1778	1.628 (1.548-1.712)	<0.0001	0.944 (0.887-1.005)	0.07	0.994 (0.934-1.058)	0.85
No Dyslipidaemia	179418	21927	18320	3369	1.611 (1.553-1.671)	<0.0001				
Dyslipidaemia	82111	10445	8559	1612	1.762 (1.671-1.858)	<0.0001	1.040 (0.975-1.108)	0.23	1.067 (1.001-1.138)	0.045
No Smoker	198398	27110	20829	4216	1.636 (1.583-1.690)	<0.0001				
Active smoker	63131	5262	6050	765	1.693 (1.569-1.828)	<0.0001	1.019 (0.938-1.106)	0.66	1.021 (0.941-1.109)	0.61
No Obesity	210624	26411	21064	3918	1.631 (1.577-1.687)	<0.0001				
Obesity	50905	5961	5815	1063	1.786 (1.673-1.908)	<0.0001	1.048 (0.974-1.127)	0.21	1.108 (1.029-1.192)	0.006
No Previous cancer	230269	24953	23284	3805	1.690 (1.633-1.749)	<0.0001				
Previous cancer	31260	7419	3595	1176	1.466 (1.378-1.559)	<0.0001	0.853 (0.795-0.915)	<0.0001	0.888 (0.828-0.953)	0.001
No Sleep apnoea syndrome	243364	29860	24888	4559	1.651 (1.600-1.704)	<0.0001				
Sleep apnoea syndrome	18165	2512	1991	422	1.702 (1.534-1.888)	<0.0001	0.995 (0.893-1.108)	0.93	1.094 (0.982-1.219)	0.10

Abbreviations Table 5: CI: Confidence Interval, COVID-19: Coronavirus Disease 2019, HR: Hazard Ratio.

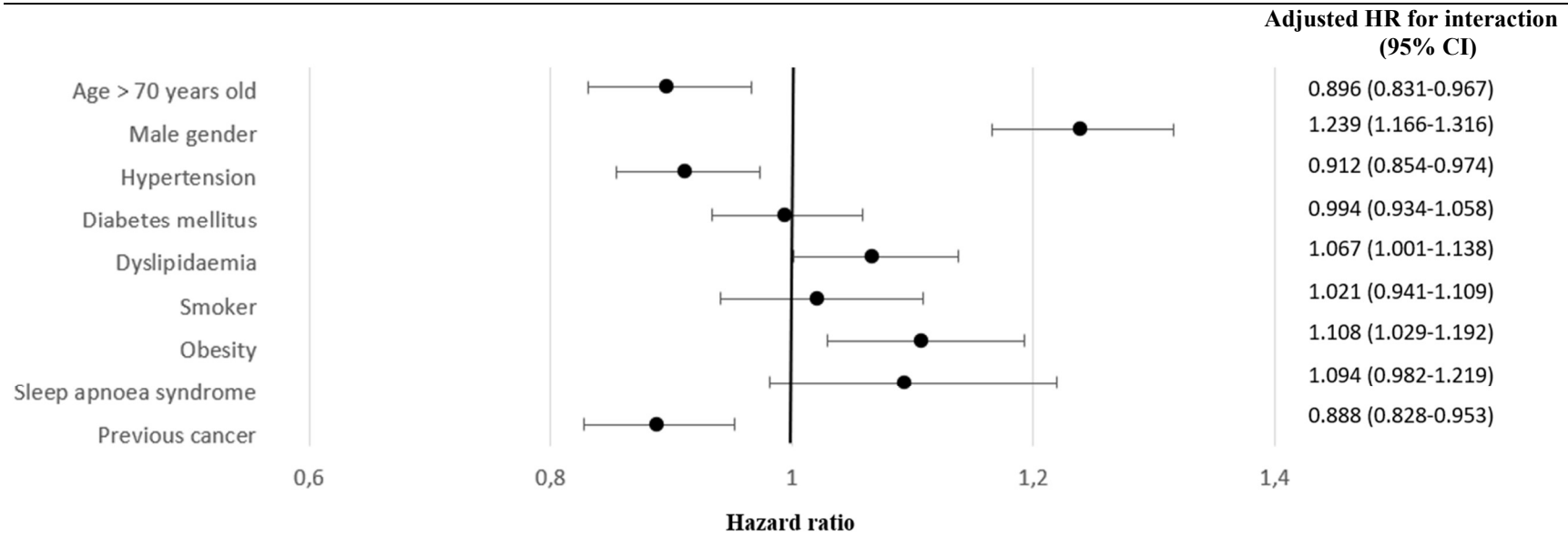


Figure 5. Forest plot of confidence intervals for sub-group analyses and interaction of risk-factors with COVID-19 for the outcome of all-cause death.

Abbreviations Figure 5: CI: Confidence Interval, COVID-19: Coronavirus Disease 2019, HR: Hazard Ratio.

4. DISCUSSION

Our study showed that there was an increase in all-cause death in AMI patients with concurrent COVID-19. Despite a higher incidence of heart failure, ischemic stroke, incident AF and VT/VF in COVID-19 patients, both adjusted and propensity-score matching analyses showed that the incidence of CV death in COVID-19 patients was significantly lower compared to COVID-19 negative patients. In other words, COVID-19 patients' death is more frequently explained by other, non-CV, causes of death, despite a higher absolute incidence/year of CV death in COVID-19 patients compared to COVID-19 negative patients.

Those results match with previous studies[17–19,21,28] that found increased CV events and complications in AMI population infected by SARS-Cov2. We can hypothesize that being infected by SARS-Cov2 during the occurrence of AMI is a marker of poor prognosis but not directly linked with CV death. This emphasizes the severity of COVID-19 in these vulnerable patients, leading to non-CV death before CV death "has a chance" to occur. This could allow clinicians to identify the most vulnerable patients that need strict CV follow-up and global care.

4.1. Strengths

Our study is the first nationwide study that included a large scale of patients with AMI and concurrent COVID-19. Systematic recruitment of AMI patients in all French facilities during almost 3 years permitted to get real-life population data, from the first French lockdown to the post-COVID-19 era. We also had a large panel of patients' characteristics despite the retrospective design of our work that confirms us that COVID-19 patients had more comorbidities and were thus more vulnerable. Considering the high number of patients in our study, to better assess the prognosis of these patients, we applied a propensity-score matching with 26 879 patients in each group that were almost completely comparable and with few events per variable, which added significant relevance to our results.

4.2. Limitations

The present study has however several limitations, mainly due to its retrospective nature. PMSI database depends on the diagnoses at hospital discharge made by physicians using ICD-10. This may lead to lack of precisions due to miscoding and possibly missing of some relevant patients' characteristics. In addition, several data are not included in this database and could have been of major interest in this study, i.e., patients' medications, time-to-hospital care, time from symptom onset to reperfusion. This risk of information bias is partly compensated by the fact that coding is linked with reimbursement and fee-for-service pricing for hospitals and thus is regularly controlled.

We only included in-hospital events and were not able to analyse data for out-of-hospital deaths, knowing that out-of-hospital cardiac arrest increased during lockdown coupled with a reduction in survival[29,30]. Yet, there are reports advocating a reduction in the number of STEMI during the COVID-19 lockdown, which may compensate this increase in out-of-hospital cardiac arrest. Besides, data about COVID-19 vaccination were not available. Of course, COVID-19 vaccines (both mRNA and viral vector vaccines) were not available in France before the end of 2020 and several months were necessary to achieve a level of vaccination deemed to offer a protection at the scale of the French population, with 25% of population who had 2 vaccine dose on June 2021, 50% on August 2021 and 77% at the end of this study on 31st January 2023[31].This missing data seems however relevant knowing that vaccination was reported to decrease stroke and AMI[32]. Of note, there are also publications advocating CV side effects following vaccination. While most described are myocarditis, some cases of AMI were also reported[33].

4.3. Subgroup analyses

Our sub-group and interaction of risk-factors analyses with COVID-19 showed a significant increase in all-cause mortality for male gender, obesity and dyslipidaemia, concordant with previous publications[34,35].

There was no difference for diabetes mellitus despite being described as an independent factor of severe COVID-19 and death in COVID-19 patients[34,36,37]. This may be explained by the

fact that no information regarding the type, i.e. type 1 or 2, and associated macro- and microvascular complications were available. The result of this lack of information could have been a major inhomogeneity of the group of diabetic patients, reducing the relevance of its interpretability. No significant difference was found for smoking and sleep apnoea syndrome, despite being described as a risk factor of COVID-19 and correlated with its severity[34,38,39].

Arterial hypertension, being aged ≥ 70 y.o. and history of previous cancer were identified as significant protective factors in our analyses. This result should also be interpreted with caution because of the lack of data about patient's medications that are potentials confounders of these subgroup analyses for arterial hypertension, in particular the modulators of the renin angiotensin aldosterone system. Data about patients with history of previous cancer advocate that this population is more vulnerable[40] and has longer stay in hospital when infected with SARS-CoV-2, but no increase in mortality or ICU admission[41]. These immunocompromised patients had net benefit from vaccination, with significant reduction in the severity of the infection[42,43], and were the top priority targets for vaccination in France from the beginning of vaccination in the end of 2020. Our results may only illustrate the efficacy of vaccination in this population leading to an improved prognosis.

Being aged ≥ 70 y.o. as a protective factor of death in COVID-19 patients could be explained by the fact that this population was also a top priority target for vaccination[44,45]. These aged patients had more comorbidities, and we can suppose that it allowed them to get a better follow-up from their doctor, more family attention during pandemic and that they were more careful to sanitary instructions against COVID-19 than younger patients who kept working and got more exposed to COVID-19 during lockdown.

4.4. Myocardial injury

In COVID-19 patients, myocardial injury, defined as an ejection fraction decline and a troponin elevation, is associated with an increased risk of in-hospital mortality[46,47]. On the opposite, the prognosis of patients with underlying CV disease but without myocardial injury is relatively favorable[47].

These data can be compared to patients' prognosis after a type 2 AMI during sepsis, with an increase in all-cause mortality, mainly non-CV mortality at short and long term[48]. During sepsis, despite marked increases in coronary blood flow, patients may have major increase in myocardial oxygen demand leading to ischemia, especially if coronary abnormalities are present. The toxic effects of TNF-α, heat shock proteins, and catecholamines can also cause troponine release.

In fact, all the CV system can be affected by COVID-19[15,46,47], with complications including myocardial injury, myocarditis, AMI, heart failure, dysrhythmias, tako-tsubo syndrome (TTS) and venous thromboembolic events[16,49]. We didn't have any data regarding thromboembolic events, myocarditis, dysrhythmias, TTS and their complication, that could have affected COVID-19 patients without being diagnosed or taken into account and may have worsened their prognosis. A recent report found in a 28 case-series patients that 40% of STEMI patients with COVID-19 had a culprit lesion that was not identifiable by coronary angiography[50], which may confound the diagnosis and management of these patients in our study.

4.5. Changes in healthcare organization and patients' behaviour

Many hypotheses could be put forward to explain increased all-cause death in AMI patients infected by SARS-Cov2. First of all, we know that there was less patients hospitalized for AMI and treated during lockdown comparatively to past years[51–56]. There was also an increase in the median time from symptom onset to reperfusion and intra-hospital mortality[17,20,23,57,58]. Delay on time to reperfusion could be explained by saturated healthcare system emergencies, protective measures for COVID-19 for all caregivers and changes in patients' behaviour because of the fear of being contaminated that led them to underestimate their symptoms and delay to consult, which could have worsened their prognosis.

Recent data are controversial with these observations, supporting a limited effect of the COVID-19 crisis on acute and 3-month outcomes of AMI patients[23]. The decrease in the number of patients admitted for AMI could be linked with a decrease of routine stress caused by work, sports activity but this hypothesis seems improbable as the anxiety rate in the French population doubled during the first lockdown compared to 2017[59].

Then, reperfusion strategy also changed during lockdown in countries like China leading to an increase in emergency intravenous thrombolysis[60]. ESC guidelines[61] for the management of acute coronary syndrome during COVID-19 pandemic kept primary PCI as the first option for STEMI and very high risk NSTEMI, delayed invasive strategy (<24h) for high risk NSTEMI and recommended coronary computed tomography angiography for intermediate and low risk NSTEMI, with fibrinolysis as a second choice. In the light of those minor changes in guidelines, we can assume that the impact for COVID-19 patients' prognosis was limited in countries such as ours.

5. CONCLUSION

In this large French nationwide cohort study, occurrence of AMI when being infected with SARS-CoV-2 increased all-cause death incidence, yet this decreased prognosis is not due to cardiovascular death. Medical follow-up of COVID-19 patients after an AMI should focus on cardiovascular events at the acute phase and then be similar to other patients since we know that their bad prognosis is not directly linked to cardiovascular death. Further investigations are needed to elucidate the main causes of death in this population.

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