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Clinical paper Long-term heart function in cardiac-arrest survivors



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Abstract

Purpose: To assess outcomes and predictors of long-term myocardial dysfunction after cardiac arrest (CA) of cardiac origin.

Methods: We retrospectively included consecutive, single-center, prospective-registry patients who survived to hospital discharge for adult out-ofhospital and in-hospital CA of cardiac origin in 2005–2019. The primary objective was to collect the 1-year New York Heart Association Functional Class (NYHA-FC) and major adverse cardiovascular events (MACE).

Results: Of 135 patients, 94 (72%) had their NYHA-FC determined after 1 year, including 75 (75/94, 80%) who were I, 17 (17/94, 18%) II, 2 (2/94, 2%) III, and none IV. The echocardiographic left ventricular ejection fraction was abnormal in 87/130 (67%) patients on day 1, 52/123 (42%) at hospital discharge, and 17/52 (33%) at 6 months. During the median follow-up of 796 [283–1975] days, 38/119 (32%) patients experienced a MACE. These events were predominantly related to acute heart failure (13/38) or ischemic cardiovascular events (16/38), with acute coronary syndrome being the most prevalent among them (8/16). Pre-CA cardiovascular disease was a risk factor for 1-year NYHA-FC > I (P = 0.01), absence of bystander cardiopulmonary resuscitation was significantly associated with NYHA-FC > I at 1 year.

Conclusion: Most patients had no heart-failure symptoms a year after adult out-of hospital or in-hospital CA of cardiac origin, and absence of bystander cardiopulmonary resuscitation was the only treatment component significantly associated with NYHA-FC > I at 1 year. Nearly a third experienced MACE and the most common types of MACE were ischemic cardiovascular events and acute heart failure. Early left ventricular dysfunction recovered within 6 months in half the patients with available values.

Keywords: Cardio-pulmonary resuscitation, Cardiac arrest, Heart failure, Ventricular ejection fraction, Prognostic factors

Introduction

Cardiac arrest (CA) is a major public health issue, with an estimated 30 000 cases annually in France alone.¹ On-scene resuscitation fails to achieve the return of spontaneous circulation (ROSC) in about three-fifths of patients. CA is usually due to medical conditions, including cardiac disease in 42% of cases.² Patients who achieve the ROSC but remain comatose are admitted to the intensive care unit (ICU).

Post-resuscitation shock is associated with both early death in the ICU and with worsening of post-anoxic lesions, often causing death after 72 hours of intensive care.³ It is due to a combination

of severe vasoplegia and post cardiac arrest myocardial dysfunction (PCAMD).⁴ Early systolic dysfunction has been documented in most CA survivors,⁵ and over a third had a left ventricular ejection fraction (LVEF) at 24 h below 40%.^{6,7} PCAMD can resolve quickly, with a third of patients whose early LVEF is below 50% recovering normal LVEF values during follow-up.⁸ However, the extent to which CA may be associated with long-term ventricular dysfunction and other adverse cardiac outcomes remains unclear. Moreover, risk factors for persistent PCAMD are not known.

The main objective of this single-center retrospective cohort study was to describe the prevalence of PCAMD and other cardio-vascular adverse events in the medium- and long-term after recovery from CA.

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Material and methods

We used the Versailles Hospital Cardiac Arrest Registry (ClinicalTrials.gov NCT03594318). Data collection was approved by the ethics committee of the French Intensive Care Society (#CESRLF_20-41), and the data were collected anonymously in compliance with French data protection legislation (French Data Protection Authority #MR004_2209691). Verbal informed consent obtained from each surrogate then from each patient who recovered consciousness was recorded in the medical file. The study is reported according to the STROBE statement.

Patients

All adults prospectively included in the Versailles Hospital Cardiac Arrest Registry between 2005 and 2019 were screened for eligibility. Inclusion criteria were out-of-hospital or in-hospital CA of cardiac origin, survival to hospital discharge, and availability of follow-up data. We excluded patients transferred outside our district and for whom no cardiologist able to provide follow-up data was identified and those transferred to a palliative care unit at ICU and/or hospital discharge.

Early patient management

All patients admitted to the ICU with ROSC and coma (defined as a Glasgow Coma Scale score < 9⁹) were managed according to current guidelines. Diagnostic tests including coronary angiography and/or brain computed tomography and/or pulmonary computed tomography angiography were performed routinely at admission, in the order dictated by the initial diagnostic probability. When these tests were uninformative, the patients underwent additional investigations including transthoracic or transesophageal echocardiography, cardiac magnetic resonance imaging, extended Holter monitoring, and endocardial electrophysiological testing.

Definitions

To define CA of cardiac origin, we used the classification proposed by Geri et al.,¹⁰ to which we added idiopathic ventricular fibrillation. The categories are as follows¹⁰: coronary pathologies (coronary syndrome, ischemic cardiopathy, and coronary spasm), structural myocardial pathologies (dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiopathy, congenital heart disease, valvular heart disease, arrhythmogenic right ventricular dysplasia), cardiac arrhythmias without morphological anomalies, and cardiac pathologies caused by an extracardiac event (toxic or metabolic). Idiopathic ventricular fibrillation was defined as CA with a shockable rhythm and no cause identified by extensive diagnostic investigations. Post-resuscitation shock was defined as the need for continuous norepinephrine or epinephrine infusion for more than 6 hours following ROSC to maintain the mean arterial pressure above 60 mmHg, despite adequate fluid loading.

PCAMD during the ICU stay was defined using quantitative echocardiographic criteria (LVEF < 50%, or < 80% of the reference LVEF, or integral time-speed < 15 cm, or LVEF < 55% during intravenous dobutamine or epinephrine treatment)¹⁴ and qualitative criteria used to describe LVEF in medical reports (e.g., "altered", "reduced", "severely altered," or "severely reduced").

Data collection

For each patient included in the registry, CA data were entered prospectively into a standardized form as previously described, ^{11,12,13} including the following Utstein criteria:¹⁴ age and sex, comorbidities, location of CA, initial rhythm, time from collapse to cardiopulmonary resuscitation (CPR) initiation (no-flow time) and from CPR initiation to ROSC (low-flow time), time from collapse to ROSC (no flow + low flow time), presence of a witness, bystander CPR, number of shocks, and epinephrine injection. The tests done to identify the cause of CA, the cause if identified, the SAPSII severity score, and in-ICU organ failures were also recorded. The following were recorded at ICU discharge and hospital discharge and at one year: survival, Cerebral Performance Category.¹⁵

To further investigate long-term cardiac outcomes and their determinants, we retrospectively collected additional data from prehospital and ICU records and, when necessary, the cardiologists and other healthcare professionals providing follow-up. Evidence of pre-CA cardiovascular disease (including ischemic heart disease. valvular heart disease, congenital heart disease, and cardiomyopathy) was sought. Patients for whom guantitative or gualitative LVEF measurements were available were classified as having or not having left ventricular systolic dysfunction, using 50% as the cutoff to distinguish between "normal" and "abnormal" LVEF, based on the recommendation of the French Society of Cardiology.¹⁶ To conduct a semi-quantitative analysis of LVEF evolution during follow-up, we combined qualitative and quantitative data from medical reports using the same threshold. Regarding gualitative measurements, LVEF described as "altered," "reduced," "severely altered," or "severely reduced" were considered to be "abnormal". Major adverse cardiovascularevents (MACE) were retrospectively collected; they included severe clinical signs of heart failure such as hospitalization for acute lung edema or worsening congestive symptoms requiring a treatment change, ischemic cardiovascular events (cerebral vascular accident, acute limb ischemia, acute coronary syndrome, significant progression of coronary disease defined as new angina or positive ischemic test in a new territory), recurrent CA of cardiac origin, and death of cardiac origin.¹⁷ Given their relevance to our study, we also included among MACE admission for rhythm or conduction disturbances and heart transplantation. To assess long-term heart function, we retrospectively collected the echocardiographic LVEF, congestive heart failure presence and severity as reflected by the New York Heart Association Functional Class (NYHA-FC)¹⁸ determined during follow-up visits while the patient was in a stable condition, whether the patient was equipped with an implantable cardioverter defibrillator, and results of ischemia tests and coronary angiograms.

Study outcomes

The primary outcome was NYHA-FC > I at 1 year (day 365 ± 30). Patients in class I were compared to those in class II, III, or IV.

Secondary outcomes included the NYHA-FC at 2 years (day 730 \pm 90), 3 years (day 1095 \pm 120), and 5 years (day 1825 \pm 180); MACE within the first post-CA year; and LVEF at 24 h, hospital discharge, and 6 months (day 180 \pm 30).

Statistical analysis

Continuous variables were described as median [interquartile range] and categorical variables as number (percentage). We compared continuous variables by applying the t test or Mann-Whitney test

and categorical variables using the chi-square test or Fisher's exact test, as appropriate. All tests were two-sided. *P* values < 0.05 were

The analyses were performed using the R program version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org).

Results

Patients

Fig. 1 is the patient flow chart. Table 1 reports the main features of the 135 study patients. CA usually occurred out of the hospital, in the presence of a witness and in a shockable rhythm. Before the CA, 42 (31%) patients had known heart disease and 14 (10%) an abnormal LVEF. Acute coronary syndrome was the most common cause of CA. Most patients received targeted temperature management at 32 °C–36 °C and required mechanical ventilation.

Myocardial function after cardiac arrest

interpreted as rejecting the null hypothesis.

The NYHA-FC at 1 year (±30 days) was available for 94/135 (72%) patients (Table 2 and Figure S1 in the Supplementary material). Four-fifths of patients reported no heart failure symptoms and nearly all the remaining patients had only mild symptoms. The proportion of class I patients decreased over time. Of the 50 patients followed to 5 years, none were class IV.

Table 3 and Figure S2 (Supplementary material) report the LVEF changes over the first 6 months after the CA. Two-thirds of patients with available LVEF values 24 hours after the CA had PCAMD. Only a third of patients still had an abnormal LVEF at 6 months.

Major adverse cardiovascular events

Of the 135 patients, 119 had a median follow-up of 796 [283–1975] days, during which 38 (32%) experienced a MACE, after a median time interval of 580 [107–1938] days (Table 4). Figure S3 (Supplementary material) shows the MACE-free survival curve. Of the 135 patients, 4 (3%) died of cardiac causes; 2 (2%) other patients underwent heart transplantation within the first year after the CA. Ischemic cardiovascular events and acute heart failure accounted for three-quarters of MACE, with acute coronary syndrome being the most frequent among them.

Variables associated with NYHA-FC > I at one year

By univariate analysis, NYHA-FC > I at 1 year was significantly associated with younger age, known heart disease before the CA, abnormal LVEF before the CA, absence of bystander CPR, and implantable cardioverter defibrillator implementation (Table 5). NYHA-FC > I was significantly associated with an abnormal LVEF at hospital discharge (P = 0.045).

Discussion

In our populations of adults with out-of-hospital and in-hospital cardiac arrest of cardiac origin, NYHA-FC > I at 1 year was significantly associated with younger age, prior known heart disease, and an abnormal LVEF at hospital discharge. The only treatment component associated with NYHA-FC > I at 1 year was absence of bystander CPR. An abnormal LVEF was documented in over two-thirds of

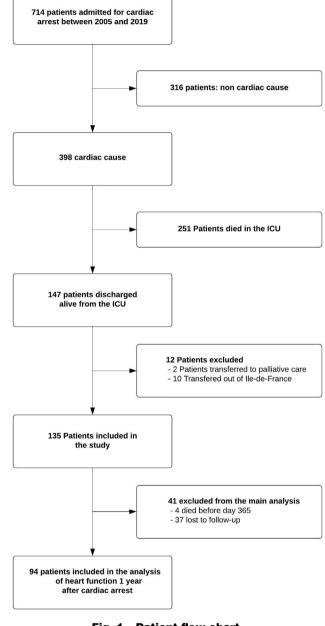


Fig. 1 - Patient flow chart.

patients at hospital discharge but only one-third at 6 months. MACE during follow-up was documented in a third of patients.

Earlier studies also found that PCAMD during the ICU stay often resolved.^{5,6} Our work added to this information by evaluating the association between early PCAMD and NYHA-FC at 1 year. We were able to perform only a univariate analysis, which showed a nearly significant association linking PCAMD in the ICU to having at least mild heart-failure symptoms at 1 year. Given the absence of a multivariate analysis, we cannot determine whether this finding was related to confounding by a prior history of heart disease or to a higher risk of PCAMD in patients with greater severity of post resuscitation syndrome.

MACE occurred in a third of patients within 5 years after the CA, with the most common types being ischemic cardiovascular events

Age, years	61 [52–72]
Males	108 (80)
BMI, kg/m ²	26.1 [23,8–29,
Diabetes	10 (7)
Medical history of heart disease	42 (31)
Known LVEF before cardiac arrest	22 (16)
With an abnormal LVEF	14 (10)
In-hospital cardiac arrest	11 (8)
Witnessed in-hospital cardiac arrest	11 (100)
Shockable rhythm	9/11 (81)
Out-of hospital cardiac arrest	124 (92)
Witnessed out-of-hospital cardiac arrest	115/124 (93)
Shockable rhythm	114/124 (92)
Bystander CPR	34/124 (27)
No flow, min	0 [0–5]
Low flow, min	12 [5–21]
Shockable rhythm	123 (91)
Epinephrine administration	36 (27)
Cumulative epinephrine dose, mg	0 [0–1]
Shocks before ROSC, n	2 [1-4]
Vasopressor infusion after ROSC	47 (35%)
SAPS II at ICU arrival, points	63 [53–71]
Coronary angiography	116 (86)
Abnormal	96/116 (83)
Significant lesions, n	2 [1–3]
Angioplasty	57/116 (49)
Causes of cardiac arrest	
Acute coronary syndrome	80 (59)
Other ischemic heart disease	19 (14)
Coronary spasm	5 (4)
Dilated cardiomyopathy	7 (5)
Hypertrophic cardiomyopathy	6 (4)
Valvular cardiomyopathy	3 (2)
Arrhythmogenic right ventricular cardiomyopathy	1 (1)
Conduction disorders	4 (3)
Long QT syndrome	1 (1)
Metabolic disorder	3 (2)
Idiopathic ventricular fibrillation	6 (4)
Post Resuscitation Shock	- ()
Inotropic use	80 (59)
Therapeutic hypothermia (32 °C-36 °C)	110 (81)
Post cardiac arrest myocardial dysfunction	87/130 (67)
LVEF, %	35 [26–44]
Renal replacement therapy	10 (7)
Mechanical ventilation	130 (96)
Duration of mechanical ventilation, days	4 [3–9]
Length of hospital stay, days	7 [4–14]

Legend: Data are medians (IQR) or numbers (%); BMI, Body Mass Index; LVEF, Left Ventricular Ejection Fraction; CPR, Cardiopulmonary Resuscitation; ROSC, Return Of Spontaneous Circulation; SAPS II, Simplified Acute Physiology Score.

and acute heart failure. In a prospective cohort study with a 1-year follow-up, a quarter of patients experienced a MACE and a third either a MACE or death from any cause.¹⁹

The prevalence of heart failure in our study was moderate but increased over time. We are aware of a single previous study providing data on heart function after CA.²⁰ A cohort of 141 patients was established prospectively, and the NYHA-FC was determined 2 weeks, 3 months, and 1 year after the CA, together with several other parameters. The proportion of patients evaluated at 1 year was similar to that in our retrospective cohort (78% vs. 72%, respectively). At 1 year, the median NYHA-FC was I and 14% of patients were class III or IV, compared to only 2% of class III patients and no class IV patients in our study. One possible explanation to this difference is that 62% of patients had a prior history of heart disease compared to only 31% in our study. The NYHA-FC improved over time, whereas it worsened in our patients. This worsening might reflect an increase in physical activities as patients recovered over time, creating oxygen needs capable of triggering symptoms of heart failure. A longitudinal follow-up study including serial measurements of left ventricular function would shed light on the reasons for NYHA-FC changes. Finally, by univariate analysis an NYHA-FC > I at 1year was significantly associated with younger age, previous known heart disease, and an abnormal LVEF before the CA. Younger patients and those with a history of heart disease may be more likely

Table 2 - New York Heart Association Functionnal Class (NYHA-FC) evolution after cardiac arrest.

Assessment date	1 year	2 years	3 years	5 years
Number of assessable patients, n	131	111	97	70
Number of patients assessed, n (%)	94 (72)	70 (63)	58 (60)	50 (71)
NYHA-FC I ^a	75 (80)	52 (74)	40 (68)	33 (66)
NYHA-FC II ^b	17 (18)	17 (24)	17 (29)	16 (32)
NYHA-FC III ^c	2 (2)	1 (2)	1 (2)	1 (2)
NYHA-FC IV ^d	0	0	0	0

Legend: Data are numbers (%).

^a No limitation of physical activity; no symptoms during normal physical activity.

^b Slight limitation of physical activity; mild symptoms during normal physical activity.

^c Marked limitation of physical activity; moderate symptoms with less than normal physical activity; comfortable only at rest.

^d Unable to carry out any physical activity without discomfort; severe symptoms with features of heart failure during minimal physical activity and even at rest.

Table 3 - Evolution in left ventricular ejection fraction (LVEF) after cardiac arrest.

Assessment day	Day 1 in-hospital	Hospital Discharge	Day 180
Total number of patients assessable	135	135 (100)	130 (96)
Semi-quantitative measurement			
Number of patients assessed	130 (96)	123 (91)	52 (40)
Normal	43 (33)	71 (58)	34 (65)
Abnormal	87 (67)	52 (42)	17 (33)
Quantitative measurement			. ,
Number of patients assessed	86 (64)	120 (89)	48 (37)
LVEF	35 (26–44)	53 (43-60)	55 (44-61)

Table 4 - Major adverse cardiological events recorded during follow	/-up.
Number of patients followed-up	119 (88%)
Follow-up time (days)	796 (283–1975)
Number of adverse events	38 (32)
Time interval	806 (285–1977)
Death from a cardiac cause	4 (3)
Time interval	730 (290–1355)
Cardiac transplantation	2 (2)
Time interval	45 (45–45)
Acute heart failure	13 (11)
Time interval	1146 (234–1980)
Ischemic cardiovascular events	16 (13)
Time interval	815 (286–1997)
Acute coronary syndrome	8 (7)
Acute limb ischemia	1 (1)
Significant progression of coronary disease	7 (6)
Rhythm or conduction disorders	3 (3)
Time interval	697 (371–1315)
Legend: Data are medians (IQR) or numbers (%); LVEF, Left Ventricular Ejection Fraction.	

to engage in physical activities capable of producing symptoms of congestive heart failure. Absence of bystander CPR was also associated with NYHA-FC > I at 1 year.

Although the retrospective design is a limitation of our study, the close collaboration between our cardiology department and community healthcare providers (cardiologists, electrophysiologists, rehabilitation therapists, and primary care physicians) allowed us to collect the primary outcome in 72% of patients, a proportion similar to that in prospective cohorts.^{19,21} Second, the single-center recruitment of the study may raise concern about selection bias. However, our pop-

ulation was similar to a prospective cohort of 1657 patients also recruited in Paris.¹⁰ Third, the NYHA-FC is not ideal for assessing heart failure, as symptoms characterizing classes II and III appear only upon exertion. Patients who avoid physical activities may thus be in class II or III yet report no symptoms. Sufficient physical activity to produce symptoms may be difficult to arrange during physician visits. Consequently, to provide further information on long-term outcomes, we collected the occurrence of MACE. MACE is a reliable outcome that is consistently described in medical files created during hospital or community care, in contrast to minor cardiovascular

	NYHA-FC = 1	NYHA-FC > 1	P-value
	n = 75 (79.8)	n = 19 (20.2)	
Age (years)	61 (52–72)	60 (51–72)	0.04
Male	56 (75)	15 (79)	0.72
BMI (kg/m²)	26.1 (24.1–29.1)	26.1 (23.9-29.1)	0.65
SAPS II	63 (54–70)	63 (54–70)	0.07
Heart disease	17 (22)	11 (58)	0.01
Heart disease and an abnormal LVEF	6 (8)	5 (26)	0.03
Bystander CPR for OHCA	20/69 (29)	1/19 (5)	0.03
No flow, min	0 (0–5)	0 (0–5)	0.13
Low flow, min	12 (5–20)	12 (5–20)	0.03
Shockable rhythm	68 (91)	17 (89)	1
Cumulative epinephrine dose	0 (0-1)	0 (0-1)	0.62
Shocks before ROSC	2 (1-4)	2 (1-4)	0.84
ACS	45 (60)	9 (47)	0.36
Maximum troponin level at Day 1	1.4 (0.5–5.6)	1.0 (0.4–5.2)	0.47
Target temperature management	61 (81)	17 (89)	0.31
PCAMD	42 (56)	16 (89)	0.06
LVEF at hospital discharge, %	54 (40-60)	53 (40-60)	0.05
Implantable cardioverter defibrillator	22 (29)	12 (63)	0.01
CPC 1 or 2 at one year	71 (95)	19 (100)	0.11

Table 5 - Variables associated at the univariable level with a NYHA-FC > 1 at one year after cardiac arrest.

Legend: Data are medians (IQR) or numbers (%); BMI, Body Mass Index; SAPS II, Acute Physiological Score II; LVEF, Left Ventricular Ejection Fraction; CPR, Cardiopulmonary Resuscitation; OHCA, out-of-hospital cardiac arrest; ROSC, Return Of Spontaneous Circulation; ACS, Acute Coronary Syndrome; PCAMD, Post Cardiac Arrest Myocardial Dysfunction; CPC, Cerebral Performance Category.

events. We did not consider data from tracking defibrillators, which include asymptomatic rhythm and conduction disorders and have been evaluated in large, randomized trials. Fourth, the proportion of patients whose LVEF was abnormal decreased from 67% on the first ICU day to 33% at 6 months, but only 40% of patients for whom this variable was available on day 1 also had an available value at 6 months. We cannot rule out that the patients without this variable at 6 months had poorer left ventricular function than did the other patients. Finally, many factors can contribute to impair heart function. Elucidation of the factors that affect the risk of heart failure after a CA would require a large-scale study. In particular, an assessment of whether the risk of PCAMD varies according to the treatment strateqy used for CA would be of interest. A major strength of our study is the reliance on a prospective registry, which provided a representative sample of patients with CA of cardiac origin. That the only patient exclusion criterion was the absence of follow-up data ensured good external validity. Our population was similar to those described in large prospective studies of CA of cardiac origin such as the TTM trial.²² Furthermore, the analysis of MACE over time added substantially to the information on heart function. The MACE-free survival analysis included nearly all the patients in the cohort (119/135), whose median follow-up was 796 [283-1975] days. The number of cardiovascular deaths was small (n = 4, 3%) but should be interpreted with caution as data on vital status were missing for 16/135 patients. Finally, the NYHA-FC status preceding cardiac arrest could not be included in our dataset due to challenges in procuring cardiology reports for patients under care across diverse private and public medical healthcare facilities, spanning hospital and outpatient settings throughout the entire Parisian area. While a number of LVEF values were extractable from imaging reports, their scarcity - as detailed in Table 1 precluded the feasibility of a statistically robust analysis addressing LVEF and NYHA-FC evolution before and after CA.

Conclusion

Most patients had no heart-failure symptoms a year after adult inhospital or out-of-hospital CA of cardiac origin, and absence of bystander CPR was the only treatment component associated with NYHA-FC > I at 1 year. Nearly a third experienced MACE, and the most common types of MACE were ischemic cardiovascular events and acute heart failure. Early left ventricular dysfunction recovered within 6 months in half the patients with available values.

CRediT authorship contribution statement

Jean-Herlé Raphalen: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. Tal Soumagnac: Writing – original draft, Writing – review & editing, Visualization. Marc Delord: Methodology, Formal analysis. Wulfran Bougouin: Methodology, Formal analysis. Jean-Louis Georges: Writing – review & editing. Marine Paul: Data curation, Writing – review & editing. Stéphane Legriel: Supervision, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

All procedures involving the patients complied with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments. In keeping with French law on retrospective analyses of deidentified health data, informed consent was not required for this study. The study database was reported to the data protection authority (Commission Nationals de l'Informatique et des Libertés, #xxxx).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.resplu.2023.100481.

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