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Research Article



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Relevance of Cardiopulmonary Resuscitation in Centenarian's Out-of-Hospital Cardiac Arrest

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Abstract

Rationale: The elderly population is growing year after year; especially individuals aged 90 and over. Centenarians account for a small proportion of out-of-hospital cardiac arrest (OHCA) victims. The CPR utility in this population is subject to debate and raises an ethical standpoint. Aims and Objectives: Our study aim is to determine characteristics associated with receipt of advanced life support (ALS) and with a return of spontaneous circulation (ROSC) among a cohort of centenarians with OHCA documented in the French National OHCA Registry (RéAC). Method: We included centenarians with OHCA recorded in the RéAC between 2011 and 2021. Clinical and demographic characteristics, OHCA context, care received, and survival were analysed. Primary outcome was the survival rate 30 days after the OHCA or upon discharge from hospital. Results: Of the 132 centenarians included, 17 had received ALS. ROSC was observed in 5 of the 17 cases. Basic life support (BLS) had been initiated by bystanders in 35.6% of cases and by firefighters in 69.2%. On arrival of the emergency medical team, asystole was noted in 91.3% of cases. Individuals having received ALS were more likely to have suffered from asphyxiation, electrocution, drowning, or an overdose (35.3%, vs. 10.5% of the non-ALS cases). Within the ALS group, ROSC was associated with the provision of BLS by bystanders (60.0%, vs. 50.0% of the cases without ROSC) or by firefighters (100.0% vs. 75.0%, respectively) and a shorter no-flow time (6 min vs. 11 min., respectively). None of the 132 included centenarians were alive 30 days after the OHCA. **Conclusion:** After OHCA in a centenarian, age appears to be a barrier to the ALS initiation but not the BLS initiation. The fact that none of the victims were alive 30 days after the OHCA raises ethical questions about the resuscitation utility for very elderly victims.

Keywords: Out-of-hospital cardiac Registry, arrest. Centenarian, Ethics, Resuscitation

Introduction

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Out-of-hospital cardiac arrest (OHCA) is a considerable public health issue in Europe and in the United States. We recently reported that the incidence of OHCA in France is 46,000 per year [1]. Even though improvements in post-OHCA care have been

observed over the last decade, the victim's prognosis remains poor; in France the day 30 survival rate ranged from 4.9% to 10.4% [1,2]. In routine clinical practice, age appears to influence the treatment of cardiac arrest; however, the decision to attempt cardiopulmonary resuscitation (CPR) or not should not be based on this variable alone [3]. Although some researchers have suggested that CPR is futile in very elderly people, we demonstrated previously that the lower survival rate observed among older OHCA victims was due

(at least in part) to a shorter duration of CPR and less intensive care (relative to that provided to younger victims [4].

The elderly population is growing year after year; this is especially true for the very oldest age groups (e.g. individuals aged 90 and over). Attitudes concerning resuscitation of elderly OHCA victims typically depend on the perceived likelihood of a successful outcome. Centenarians account for a small proportion of OHCA victims - less than 1% in France[5]. Although post-OHCA survival rates in older adults vary widely in the literature, the utility of CPR in this population is subject to debate [6-11]. The resuscitation of elderly OHCA victims (and especially centenarians) must be considered from an ethical standpoint. The primary objective of the present study was to describe a cohort of centenarian OHCA victims documented in the French National OHCA Registry (RéAC). The study's secondary objectives were to determine the characteristics of individuals who received advanced life support (ALS) and those with a return of spontaneous circulation (ROSC).

Methods

Study setting

The study data were extracted from the RéAC registry, which gathers data on OHCAs dealt with by French mobile intensive care units (MICUs) [12]. In France, the prehospital emergency system has two tiers. The first professional responders are usually firefighters, who arrive rapidly on the scene and provide basic life support (BLS). The MICU (comprising at least an ambulance driver, a nurse, and a senior emergency physician) then arrives and can provide advanced life support (ALS)[13]. In the hospitals that are part of the RéAC network, a member of the MICU fills out a specific OHCA intervention form; the latter follows the Utstein resuscitation template[14] and complies with the French emergency medical services' requirements.

Participants and data

Data were collected between July 1st, 2011, and September 1st, 2021. We included all OHCA victims aged 100 or over and then extracted data on the OHCA, the provision of BLS by bystanders and/or by firefighters, the provision of ALS, and the survival rate 30 days after the OHCA or upon discharge from hospital (the primary endpoint). The other endpoints were the frequency of ROSC, the survival rate on admission to hospital on day 0, and the frequency of a good neurologic outcome in day 30 survivors. A good neurological outcome was defined as Cerebral Performance Category of 1 or 2[15].

Statistical analysis

We firstly described the population of people aged 100 years and over. Then, we compared patients who received ALS with those who did not (ALS+ vs ALS-). Finally, we compared patients who sustained a ROSC with patients who did not (ROSC+ vs. ROSC-).

For quantitative variables, the normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Non-normally distributed quantitative variables were described as the median (1st quartile Q1; 3rd quartile Q3). Qualitative variables were described as the frequency (percentage). Depending on the variable's distribution, our bivariate analyses involved Pearson's khi-2 test, Fisher's exact test, or a nonparametric Mann-Whitney U test. All tests were two-sided, and the threshold for statistical significance was set to p<0.05. All analyses were performed using SPSS software (version 25.0, IBM, Armonk, NY, USA).

Ethics

The study was approved by the French Advisory Committee on Information Processing in Health Research (Comité consultatif pour le traitement de l'information en matière de recherche dans le domaine de la santé, Paris, France) and the French National Data Protection Commission (Commission nationale de l'informatique et des libertés (Paris, France): authorization number: 910946). In line with the French legislation on retrospective studies of registry data, patient consent was neither required nor sought.

Results

The study population

During the study period, the RéAC registry included 130,678 OHCA victims, of which 132 were aged 100 or over and were included in the present study. Seventeen of the 132 OHCA victims received ALS, which led to ROSC in five cases (Figure 1). The median age of the overall study population was 101 years, and 71.2% of the OHCA victims were men. OHCA mainly occurred at home (in 69.2% of cases) and was due to an underlying medical condition or disease (85.6%). A bystander was present at the time of the OHCA in 74.2% of cases and provided BLS in 35.6% of cases. A first professional responder (i.e. a firefighter) provided BLS in 68.2% of cases, and the MICU provided ALS in 12.9% of cases. The first cardiac rhythm recorded by the MICU was asystole in 91.3% of cases. The time interval between collapse and the arrival of the first professional responder was 9 minutes, and the time interval between collapse and the MICU's arrival was 20 minutes. ROSC was observed in 6 cases (4.5%) and five patients were admitted alive to the hospital; hence, the day 0 survival rate was 3.8%. The day 30 survival rate was zero (i.e. no survivors).



Figure 1: Study flowchart.

Characteristics of the patients having received ALS

Patients having received ALS were more likely to have a history of cardiovascular disease (82.4%, vs. 45.2% in cases not given ALS, p=0.008). The OHCAs in the ALS group were more likely to have been caused by overdose, asphyxia, drowning or electrocution (35.3%, vs. 10.5% in cases not given ALS; p=0.013) and less likely to have been caused by a medical cause or by trauma (64.7% vs. 88.7%, respectively; p = 0.018). Patients having received ALS were less likely to be at the end of life (0.0%, vs. 11.3% in the non-ALS group) but the intergroup difference was not significant. "Do not resuscitate" orders were noted for one patient in the ALS group and 5 in the non-ALS group. The presence of a bystander was more frequent in the ALS group (88.2%, vs. 72.2% in the non-ALS group); this bystander was more likely to be a family member (52.9% vs. 40.9%, respectively) and was more likely to initiate BLS (52.9% vs. 33.0%, respectively). ALS always included intubation and usually included an epinephrine injection (in 70.6% of cases). The provision of ALS was associated with a shorter arrival time for the firefighters (8 vs. 10 min in the non-ALS group) and for the MICU (13 vs. 20 min, respectively), and a shorter no-flow time (7 vs. 12 min, respectively). The two groups did not differ significant with regard to the person's location at the time of the OHCA; this was notably true for being in a nursing home (23.5% in the ALS group and 22.3% in the non-ALS group). The provision of ALS was associated with a significantly greater frequency of ROSC (29.4%, vs. 0.9% in the non-ALS group; p<0.001) and the D0 survival rate (29.4% vs. 0.0%, respectively; p<0.001). The day 30 survival rate was zero in both the ALS and non-ALS groups.

	Overall population	ALS	No ALS	р
n	132	17	115	
Sex (% men)	38/132 (71.2)	13/17 (76.5)	81/115 (70.4)	0.777
Age	101 [100;102]	101 [100;102]	101 [100;102]	0.582
Location of OHCA				
- Home	83/120 (69.2)	11/17 (64.7)	72/103 (69.9)	
- Nursing Home	27/120 (22.5)	4/17 (23.5)	23/103 (22.3)	NA
- Public place	3/120 (2.5)	1/17 (5.9)	2/103 (1.9)	
- Other location	7/120 (5.8)	1/17 (5.9	6/103 (5.8)	

Medical history:				
- Cardiovascular disease	66/132 (50.0)	14/17 (82.4)	52/115 (45.2)	0.008
- Respiratory disease	13/132 (9.8)	2/17 (11.8)	11/115 (9.6)	NA
- Diabetes	5/132 (3.8)	1/17 (5.9)	4/115 (3.5)	NA
- End of life	13/132 (9.8)	0/17 (0.0)	13/115 (11.3)	NA
- Other disease	32/132 (24.2)	3/17 (17.6)	29/115 (25.2)	0.762
DNR order	6/132 (4.5)	1/17 (5.9)	5/115 (4.3)	NA
Etiology of the OHCA				
- Medical	113/132 (85.6)	11/17 (64.7)	102/115 (88.7)	0.018
- Traumatic	1/132 (0.8)	0/17 (0.0)	1/115 (0.9)	NA
- Other (overdose, asphyxia, drowning or electrocution)	18/132 (13.6)	6/17 (35.3)	12/115 (10.5)	0.013
Bystander presence at collapse				
- witness	98/132 (74.2)	15/17 (88.2)	83/115 (72.2)	0.236
- first aid provider or MMT	14/132 (10.6)	1/17 (5.9)	13/115 (11.3)	NA
Type of witness				
- Family	56/132 (42.4)	9/17 (52.9)	47/115 (40.9)	
- Healthcare professional	8/132 (6.1)	0/17 (0.0)	8/115 (7.0)	NA
- First aid	49/132 (37.1)	7/17 (41.2)	42/115 (36.5)	
- Other	19/132 (14.4)	1/17 (5.9)	18/115 (15.7)	
Provision of BLS by a bystander:				
- CC only	30/132 (22.7)	3/17 (17.6)	14/115 (12.2)	
- CC + ventilation	17/132 (12.9)	6/17 (35.3)	24/115 (20.9)	NA
- No BLS	85/132 (64.4)	8/17 (47.1)	77/115 (67.0)	
Provision of BLS by the first professional responder	90/132 (68.2)	15/17 (88.2)	75/115 (65.2)	0.091
AED used before the MICU's arrival	79/132 (59.8)	14/17 (82.4)	65/115 (56.5)	0.062
AED shock before MICU's arrival	0/132 (0.0)	0/17 (0.0)	0/115 (0.0)	
First recorded rhythm at MICU arrival				
- asystole	116/127 (91.3)	14/16 (87.5)	102/111 (91.9)	
- PEA	4/127 (3.1)	0/16 (0.0)	4/111 (3.6)	NA
- VF/VT	0/127 (0.0)	0/16 (0.0)	0/111 (0.0)	
- ROSC due to BLS	7/127 (5.5)	2/16 (12.5)	5/111 (4.5)	

ALS initiated	17/132 (12.9)	NA	NA	
Intubation	17/132 (12.9)	17/17 (100.0)	0/111 (0.0)	NA
Epinephrine	12/132 (9.1)	12/17 (70.6)	0/115 (0.0)	
If Epinephrine, dose	4 [2;5]	4 [2;5]	NA	NA
Shock by MICU's	1/132 (0.9)	1/17 (5.9)	0/115 (0.0)	NA
Times - T0 to arrival of the first professional responder (firefighters)	9 [5;14]	8 [6;12]	10 [5;15]	0.999
- T0 to arrival of the MICU				
- No-flow time	20 [12;27]	13 [10;27]	20 [12;28]	0.366
- Low-flow time	11 [4;20]	7 [3;13]	12 [4;20]	0.163
	14 [5;24]	23 [17;37]	11 [4;23]	0.001
Survival				
- ROSC	6/132 (4.5)	5/17 (29.4)	1/115 (0.9)	NA
- Dead on scene	127/132 (96.2)	12/17 (70.6)	115/115 (100.0)	< 0.001
- D0 survival	5/132 (3.8)	5/17 (29.4)	0/115 (0.0)	NA
- D30 Survival	0/132 (0.0)	0/17 (0.0)	0/115 (0.0)	NA
- If alive, CPC 1-2	NA	NA	NA	NA

Data are quoted as the frequency (percentage) for qualitative variables or the median [1st quartile; 3rd quartile] for quantitative variables. NA: not applicable, DNR: do not resuscitate, BLS: basic life support, CC: chest compression, AED: automated external defibrillator, PEA: pulseless electrical activity, VT/VF: ventricular tachycardia/ventricular fibrillation, No-flow : time between T0 and first cardiopulmonary resuscitation, Low-flow: time between the first cardiopulmonary resuscitation and end of resuscitation, ROSC: return of spontaneous circulation, ALS: advanced life support, T0: time of the call to the emergency services, MICU: mobile intensive care unit, CPC: cerebral performance category

Table 1: Description of the study population as a whole and the ALS and non-ALS subgroups.

Characteristics of patients with ROSC

ROSC was noted in five of the 17 patients in the ALS group (Table 2). The small sample size prevented us from performing a statistical analysis. In the ROSC group, the OHCA was more likely to have occurred at home (80.0%, vs. 58.3% in the non-ROSC group) and less likely to have occurred in a nursing home (0.0% vs. 33.3%, respectively). The presence of a family member bystander was more likely in the ROSC group (80.0%) than in the non-ROSC group (41.7%). Patients with ROSC were more likely to suffer from an OHCA another cause of OHCA (other than medical or traumatic etiology, ie. overdose, asphyxia, drowning or electrocution) and more likely to receive bystander BLS (60.0%, vs. 40.0% in the non-ROSC group) or firefighter BLS (100.0% vs. 83.3%, respectively). In the ROSC group, the first cardiac rhythm recorded by MICU was less likely to be asystole (80.0%, vs. 90.9% in the non-ROSC group), and patients were more likely yo receive epinephrine was more often injected (80.0% vs. 66.7%, respectively). ROSC was associated with a shorter no-flow time (6 min, vs. 11 min in the non-ROSC group) and a longer low-flow time (22 vs. 13 min, respectively). All patients with a ROSC were admitted alive to hospital but none survived to D30.

	Population	ROSC +	ROSC -
n	17	5	12
Sex (% men)	13/17 (76.5)	4/5 (80.0)	9/12 (75.0)
Age	101 [100;102]	101 [100;101]	101 [100;102]
Location of OHCA			
- Home	11/17 (64.7)	4/5 (80.0)	7/12 (58.3)
- Nursing Home	4/17 (23.5)	0/5 (0.0)	4/12 (33.3)
- Public place	1/17 (5.9)	1/5 (20.0)	0/12 (0.0)
- Other location	1/17 (5.9)	0/5 (0.0)	1/12 (8.3)
Medical history:			
- Cardiovascular disease	14/7 (82.4)	4/5 (80.0)	10/12 (83.3)
- Respiratory disease	2/17 (11.8)	0/5 (0.0)	2/12 (16.7)
- Diabetes	1/17 (5.9)	0/5 (0.0)	1/12 (8.3)
- End of life	0/17 (0.0)	0/5 (0.0)	0/12 (0.0)
- Other disease	3/17 (17.6)	1/5 (20.0)	2/12 (16.7)
DNR order	1/17 (5.9)	0/5 (0.0)	1/12 (8.3)
Etiology of the OHCA			
- Medical			
- Traumatic	11/17 (64.7)	1/5 (20.0)	10/12 (83.3)
- Other (overdose, asphyxia, drowning or	0	0	0
electrocution)	6/17 (35.3)	4/5 (80.0)	2/12 (16.7)
Bystander presence at collapse			
- witness	15/17 (88.2)	5/5 (100.0)	10/12 (83.3)
- first aid provider or MICU	1/17 (5.9)	0/5 (0.0)	1/12 (8.3)
Type of bystander			
- Family member	9/17 (52.9)	4/5 (80.0)	5/12 (41.7)
- Healthcare professional	7/17 (41.2)	1/5 (20.0)	6/12 (50.0)
- other	1/17 (5.9)	0/5 (0.0)	1/12 (8.3)

Provision of BLS by a bystander:			
- CC only	6/17 (35.3)	3/5 (60.0)	3/12 (25.0)
- CC + ventilation	3/17 (17.6)	0/5 (0.0)	3/12 (25.0)
- No BLS	8/17 (47.1)	2/5 (40.0)	6/12 (50.0)
Provision of BLS by the first professional responder	15/17 (88.2)	5/5 (100.0)	10/12 (83.3)
AED used before the MICU's arrival	14/17 (82.4)	5/5 (100.0)	912 (75.0)
First recorded rhythm at MICU arrival			
- asystole	15/16	4/5 (80.0)	10/11 (90.9)
- ROSC after BLS	2/16 (12.5)	1/5 (20.0)	1/11 (9.1)
ALS initiated	17/17 (100.0)	5/5 (100.0)	12/12 (100.0)
Intubation	17/17 (100.0)	5/5 (100.0)	12/12 (100.0)
Epinephrine	12/17 (70.6)	4/5 (80.0)	8/12 (66.7)
If Epinephrine, dose	4 [2;5]	4 [2;5]	3 [2;4}
Times			
T0 to arrival of the first professional responder (firefighters)	8 [6;12]	9 [6;11]	8 [6;13]
T0 to arrival of the MICU	20 [12;27]	22 [10;40]	20 [12;26]
No-flow time	11 [4;20]	6 [0;19]	11 [4;20]
Low-flow time	14 [5;24]	22 [13;36]	13 [5;24]
Survival			
- ROSC	5/17 (29.4)	5/5 (100.0)	0/12 (0.0)
- Dead on scene	12/17 (70.6)	0/5 (0.0)	12/12 (100.0)
- D0 survival	5/17 (29.4)	5/5 (100.0)	0/12 (0.0)
- D30 Survival	0/17 (0.0)	0/5 (0.0)	0/12 (0.0)
- If alive, CPC 1-2	-	-	-

Data are quoted as the frequency (percentage) for qualitative variables or the median [1st quartile; 3rd quartile] for quantitative variables. NA: not applicable, DNR: do not resuscitate, BLS: basic life support, CC: chest compression, AED: automated external defibrillator, PEA: pulseless electrical activity, VT/VF: ventricular tachycardia/ventricular fibrillation, ROSC: return of spontaneous circulation, ALS: advanced life support, T0: time of the call to the emergency services, MICU: mobile intensive care unit, CPC: cerebral performance category

Table 2: Characteristics of OHCA victims with or without ROSC.

Discussion

To the best of our knowledge, few researchers have studied OHCAs in centenarians. Our study of 132 individuals highlighted the strong levels of commitment from all the players in the survival chain: bystanders, first professional responders (firefighters) and MICUs. Thanks to their efforts, 29.4% of the victims were resuscitated by the MICU and arrived alive at hospital. Unfortunately, the day 30 survival rate was zero.

CPR initiation

In our study, BLS was provided by bystanders in 35.6% of cases and by firefighters in 68.2% of cases. These surprisingly high rates are close to those observed for OHCA victims in general. In a population with a median age of 67 years, BLS had been performed by bystanders in about 50% of cases and by firefighters in about 80% [16,17]. However, the frequency of ALS initiation by the MICU (12.9% in our study) was far lower than in a general population of OHCA victims (~70%) [17]. Hence, age does not seem to be a barrier for BLS but is for ALS. This finding is probably related to the MICU physician's medical responsibility [13].Indeed, he/she has to assess the patient's condition and to decide when to stop resuscitation efforts. Moreover, the provision of ALS in our study was associated with a shorter no-flow time. This might be related to another finding of the present study; the MICU was more likely to provide ALS when victim has an acute cause of OHCA. Indeed, there are many more causes designated as "other" in the group of resuscitated patients (35.5% of cases, vs. 10.5% of OHCAs with a medical cause). Most of these OHCAs were caused by food ingested into the bronchial system. This result is comparable with Kitamura et al. one who observed in a resuscitated population a 9.3% rate of external cause of the cardiac arrest [18]. These results suggest that age is associated with the initiation of ALS; the MICU was more likely to initiated CPR when the OHCA had an external or transient causes, rather than a medical cause. One can consider that a centenarian victim of an OHCA with an external or transient cause might have been in good physical condition and that ethical considerations prompted the MICU physician to intervene. In contrast, the the MICU physician might have decided not to intervene when the OHCA was caused by an underlying medical condition in a very elderly person. This hypothesis is supported by our comparison of individuals with vs. without ROSC after the receipt of ALS. In patients with ROSC, the OHCA was mainly due to a non-medical cause (food asphyxiation) and often occurred at home – suggesting that these victims were more independent and perhaps had a better chance of survival.

Low survival factors

It is known that older age is associated with poor survival. Furthermore, in our study population of centenarians, the cardiac rhythm initially observed by the MICU on arrival was usually asystole – another factor known to be associated with poor survival. This finding might also explain (at least in part) the MICU physician's decision to not resuscitate some patients. The prevalence of a shockable rhythm was lower our study than in other studies (2.5% according to Kitamura et al [18]. and 5.0% according to Deasy et al [8]. This difference might be due to the fact that in our study, (i) bystander BLS was initiated in less than 50% of cases, and (ii) the MICU team arrived on scene 20 minutes after the OHCA onset (vs. 8 minutes in Kitamura et al.'s study and 7 minutes in Deasy et al.'s study). Indeed, it is well known that an initially shockable rhythm will disappear in the absence of rapid CPR or defibrillation [8-18].

Ethical considerations

Our study results raise several important ethical questions. We noted that six patients had given a "do not resuscitate" (DNR) order. One of the six nevertheless received ALS. We hypothesize that the MICU was not aware of the DNR order or that family members had insisted on the provision of ALS. This is a very important issue because family members are not necessarily prepared to see their loved one die. Until this point, the ethical question was "is it ethical to attempt to resuscitate a centenarian who has no chance of even short-term survival?". However, the MICU team also has to deal with a request for resuscitation by family members. The MICU's physician might also feel that an attempted resuscitation will help the family with their subsequent bereavement; we believe that this ethical consideration must also be taken into account. Moreover, the patient does not always sufficiently communicate his or her intentions regarding resuscitation to healthcare providers or to family members [19, 20].

Global survival

Lastly, we found that regardless of ALS provision or ROSC, the 30-day survival rate was zero. All the patients with ROSC were alive upon hospital admission but died within 30 days. The 30-day survival rates in Deasy et al.'s study and Kitamura et al.'s study were 2.5% and 1.1% [8, 18].It is necessary to consider that intensive care unit admission of resuscitated patients is expensive. These issues must be taken into account by the expert groups and ethics forums that advise the health authorities on resuscitation guidelines.

Limitations

Our study had some limitations. Firstly, the French National OHCA registry only includes data on prehospital care but not on in-hospital decisions that might have influenced the patients' survival. However, this is limitation applies to all studies based on registry data. Secondly, we studied the French prehospital system for OHCA care; our results might not be generalizable to other countries and/or other organizational systems. Thirdly, the small number of patients with ROSC after ALS prevented us from performing a statistical analysis. However, our overall study population of centenarian OHCA victims is one of the largest described to date, and we observed some interesting trends in the subgroups.

Conclusion

Cardiac arrest in the centenarian presents a number of real ethical issues. On one hand, the extremely low survival rates observed here raise the question of whether resuscitation is ethically justified. On the other hand, it does not seem fair to withhold treatment when the OHCA is not related to an underlying medical condition and/or when the victim collapses in front of their family. In view of the scarcity of literature data on this topic, we encourage other OHCA registries to assess and report on these issues and thus provide a solid basis for resuscitation guidelines.

Author Contributions

E. Wiel: (1) the conception and design of the study, acquisition of data, analysis and interpretation of data, (2) drafting the article (3) final approval of the version to be submitted and (4) agreement to be accountable for all aspects of the work. V. Canon: (1) the conception and design of the study, acquisition of data, analysis and interpretation of data, (2) drafting the article (3) final approval of the version to be submitted and (4) agreement to be accountable for all aspects of the work. N. Segal: (1) the acquisition of data (2) revising the article critically for important intellectual content, (3) final approval of the version to be submitted and (4) agreement to be accountable for all aspects of the work C. Di Pompeo: (1) the acquisition of data (2) revising the article critically for important intellectual content, (3) final approval of the version to be submitted and (4) agreement to be accountable for all aspects of the work. H. Hubert: (1) the conception and design of the study and the acquisition of data (2) revising the article critically for important intellectual content, (3) final approval of the version to be submitted and (4) agreement to be accountable for all aspects of the work.

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