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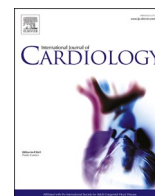
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Registered prodromal symptoms of out-of-hospital cardiac arrest among patients calling the medical helpline services

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ABSTRACT

Background

Early identification of warning symptoms among out-of-hospital cardiac arrest (OHCA) patients remains challenging. Thus, we examined the registered prodromal symptoms of patients who called medical helpline services within 30-days before OHCA.

Methods

Patients unwitnessed by emergency medical services (EMS) aged ≥ 18 years during their OHCA were identified from the Danish Cardiac Arrest Registry (2014–2018) and linked to phone records from the 24-h emergency helpline (1–1–2) and out-of-hours medical helpline (1813-Medical Helpline) in Copenhagen before the arrest. The registered symptoms were categorized into chest pain; breathing problems; central nervous system (CNS)-related/unconsciousness; abdominal/back/urinary; psychiatric/addiction; infection/fever; trauma/exposure; and unspecified (diverse from the beforementioned categories). Analyses were divided by the time-period of calls (0–7 days/8–30 days preceding OHCA) and call type (1–1-2/1813-Medical Helpline).

Results

Of all OHCA patients, 18% (974/5442) called helpline services (males 56%, median age 76 years [Q1–Q3:65–84]). Among these, 816 had 1145 calls with registered symptoms. The most common symptom categories (except for unspecified, 33%) were breathing problems (17%), trauma/exposure (17%), CNS/unconsciousness

Abbreviations: ATC, Anatomical Therapeutic Chemical; HF, Heart failure; COPD, Chronic obstructive lung disease; CPR, Cardiopulmonary resuscitation; CNS, Central Nervous System; EMS, Emergency medical services; ESCAPE-NET, The European Sudden Cardiac Arrest network towards Prevention, Education, New Effective Treatment; GP, General practitioner; ICD, International Classification of Disease; IHD, Ischemic heart disease; ISCED, International Standard Classification of Education; OHCA, Out-of-hospital cardiac arrest; ROSC, Return of spontaneous circulation.

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(15%), abdominal/back/urinary (12%), and chest pain (9%). Most patients (61%) called 1813-Medical Helpline, especially for abdominal/back/urinary (17%). Patients calling 1–1-2 had breathing problems (24%) and CNS/unconsciousness (23%). Nearly half of the patients called within 7 days before their OHCA, and CNS/unconsciousness (19%) was the most registered. The unspecified category remained the most common during both time periods (32%;33%) and call type (24%;39%).

Conclusions

Among patients who called medical helplines services up to 30-days before their OHCA, besides symptoms being highly varied (unspecified (33%)), breathing problems (17%) were the most registered symptom-specific category.

1. Introduction

Despite improvements over time, including the implementation of bystander cardiopulmonary resuscitation (CPR) programs and the use of automated external defibrillators, the survival chances among out-of-hospital cardiac arrest (OHCA) patients remain low. [1] To increase the survival chance, a key factor would be to prevent the occurrence of a cardiac arrest among patients at risk of OHCA, which remains challenging. Therefore, it is crucial to identify warning symptoms before OHCA that warrant public recognition and early action by emergency medical personnel and physicians to detect patients at high risk.

Approximately half of the individuals who suffer an OHCA are not diagnosed with traditional cardiovascular risk factors, which makes it challenging to identify them and initiate prophylactic measures. [2] Nevertheless, recent studies have shown that OHCA patients had contact with the healthcare system, [3–5] and often experienced prodromal symptoms (including chest pain, dyspnea) from minutes to days or months before OHCA. [6–8] The existing studies have interviewed survivors from OHCA, bystanders on-site, or used information documented by the emergency medical services (EMS) in the field. Thus, the data collection on prodromal symptoms was obtained after the occurrence of OHCA, and in selected populations, introducing the risk of recall bias and yielding results that are not representative of the population at large. [7–1] Although contact with the pre-hospital system is of considerable importance, little is known of the symptoms that individuals report when calling the medical non-emergency or emergency helpline services. In the Capital Region of Denmark, we have a unique opportunity to avoid recall bias by using the electronic records of calls to the out-of-hours medical services (1813-Medical Helpline) for non-emergency conditions and emergency calls to the EMS dispatch center (1–1-2). This data contains information on symptoms registered by healthcare professionals before OHCA. The study aimed to describe symptoms registered by healthcare professionals from calls to the emergency and non-emergency medical helpline services up to 30 days before their OHCA.

2. Methods

2.1. Study setting and registered symptoms

In the Capital Region of Denmark, residents with non-emergency medical conditions who cannot reach their general practitioner (GP) call the 1813-Medical Helpline from 4 p.m. until 8 a.m., during weekends and public holidays. The 1813-Medical Helpline is staffed by trained nurses and doctors who provide advice or refer to emergency departments. [11] In case of a medical emergency, residents can dial the 24 h emergency number 1–1-2, where dispatchers (doctors, nurses, and paramedics) evaluate the urgency and prioritize the dispatch of ambulances.

The 1–1-2 and the 1813-Medical Helpline is an integrated service located at one facility, the Copenhagen EMS. [12] For each call, the healthcare professionals (supported by Danish Index) assess the main reason for calling among a total of 37 chief complaint groups. Each are subdivided into five levels of emergency (A-E). In case of life-threatening

symptoms, the decision support tool indicates the highest level of emergency (A). [13] A similar decision support tool is also used by the 1813-Medical Helpline to determine appropriate aid. [11] In both cases, during the telephone triage healthcare professionals follow a flowchart according to the decision support tool, which ensures that, everyone is inquired systematically about their complaint.

It is important to note that healthcare professionals only register one chief complaint per call, even if patients reported several complaints. To describe prodromal symptoms, we used these chief complaint groups originally registered by the healthcare professional. For analysis we divided them into 8 main categories: (1) chest pain, (2) breathing problems, (3) Central Nervous System (CNS)-related symptoms including episodes of unconsciousness (CNS/unconsciousness), (4) symptoms from the abdominal/back/urinary tract (abdominal/back/urinary), (5) psychiatric/addiction-related problems (psychiatric/addiction), (6) infection/fever, (7) trauma/exposure and (8) unspecified (Supplementary Table S1). The latter contains a diverse group of chief complaints that did not fit into any of the others, for example, unclear problems, a complication of a known disease, etc. In some cases, the healthcare professionals did not register a chief complaint (“no registered symptom”), and we did not include them in the main analyses.

2.2. Data sources

In Denmark, all residents have a unique civil registration number, enabling linkage between the nationwide Danish registries on an individual level. [14] We used data from electronic records of calls to the medical helpline services from 1st January 2014 to 31st December 2018. This register contains information on the time and date when the healthcare professionals received a call, the chief complaint using two different criteria-based systems (respectively for 1–1-2 and 1813-Medical Helpline), and ultimately what response (including information on dispatch of ambulances or other vehicles), treatment or advice was given during the call, as described also elsewhere. [11]–[13] OHCA patients in the Capital Region of Denmark were identified from the national register, Danish Cardiac Arrest Register (2014–2018). [1] This register includes the date, location of OHCA (private home or public place), witnessed status (by a bystander, EMS, or unwitnessed), bystander-performed CPR and defibrillation, first recorded heart rhythm, and survival status on hospital arrival.

From the Danish National Patient Register, we retrieved diagnose codes, according to the International Classification of Disease (ICD 10), from the emergency department, inpatient, and outpatient hospital admissions (Supplementary Table S2). [15] Information on all redeemed medical prescriptions was obtained from the Danish National Prescription Register with drugs classified according to the Anatomical Therapeutic Chemical (ATC) system (Supplementary Table S2). [16] Diagnose codes up to 10 years before OHCA were used to define comorbidities and the redeemed prescriptions within 180 days before OHCA were used to define the patient’s therapy. Separately, we examined the redeemed prescriptions and hospital discharge diagnoses within 180 days before the date of the call, to examine each prodromal symptom related to a previous medication or hospital discharge diagnosis. For antibiotics and QT-prolonging drugs we included prescriptions filled 30 days before the

index date (OHCA date and call date), as usually are prescribed for short periods. Information on age, sex, and vital status were obtained from the Danish Civil Registration System. [17] While causes of death was obtained from death certificates from the National Causes of Death Register. [18] To study the socioeconomic status among OHCA patients we used the household income and the education level of the patient, which was calculated as a 5-year average income meaning 5 years preceding (and excluding) the year of OHCA and divided into tertiles (low, medium, and high income). This, to take yearly variations into account due to the potential influence of acute disease. Information on the educational level was obtained from the Population's Education Register [19] and categorized into three groups by the International Standard Classification of Education (ISCED) [20] levels: (1) Basic education, (2) General or vocational upper secondary, and (3) Bachelor, Master and Doctoral Degree or equivalent. Individuals with no information on education level or income were added respectively to the group (1) of education levels and in the low-income, as missing values were assumed to be in the lower education and income group.

2.3. Population and study design

This is a retrospective, registry-based cohort study. We included all OHCA patients of presumed cardiac cause, 18 years of age or older, and not EMS-witnessed between January 1st, 2014, and December 31st, 2018 in the Capital Region of Denmark. They were linked to electronic call records within 30 days before OHCA. EMS-witnessed arrests were excluded to obtain a more homogenous population as they differ from the rest of the OHCA. This is because EMS-witnessed arrests are considered a subset of OHCA, where the majority had a preexisting cardiac or respiratory disease and experienced prodromal symptoms before EMS personnel arrived, leading to higher survival rates. [21]

Supplementary Fig. S1 illustrates all calls included in the analysis. We aimed to identify registered prodromal symptoms among patients that called before experiencing an OHCA, which represents the general OHCA population. Therefore, excluded the call related to the OHCA event — the one resulting in an ambulance dispatch on the OHCA date, as made after or during an OHCA.

2.4. Statistics

Descriptive statistics were used to summarize categorical variables and medians with interquartile ranges (IQR) for continuous variables. Analyses of symptoms were made including all the calls with a registered symptom where one patient could have multiple calls. To analyze the baseline characteristics among OHCA patients, these patients were included in the analyses only once. Analyses were divided according to the time period (0–7 days or 8–30 days before OHCA) and the call type (either 1–1-2 or 1813- Medical Helpline). The cut-offs of 7 and 30 days were chosen to investigate the prodromal symptoms of OHCA, as previous studies have shown that patients had experienced symptoms shortly before OHCA. [8,9] When analyzing the characteristics of patients according to the registered prodromal symptoms, among patients with more than one call, the priority was given to chest pain, followed by this order: breathing problems, CNS/unconsciousness, abdominal/back/urinary, psychiatric/addiction, infection/fever, trauma/exposure and unspecified. This is based on the already described prodromal symptoms from minutes to days or months before OHCA. [6–8].

Separately, we analyzed differences in the registered prodromal symptoms and patient characteristics among those calling multiple times, according to the number of calls, subdivided into 3 groups: “1 call”, “2 calls” and “≥3 calls”. Finally, we examined differences in the registered prodromal symptoms according to sex and age, where age was categorized as ≤65 or > 65 years old. Data management and analyses were performed with R version 3.6.1. [22]

2.5. Ethics

The study was approved by the Danish Data Protection (Agency Ref. no 3–3013-2795/1, local ref.no. P-2019-191). The information on the study population was encrypted and rendered anonymous by Statistics Denmark, and registry-based studies do not require ethical approval.

3. Results

There were 5442 patients with OHCA in the Capital Region of Denmark from 2014 to 2018. Among these, 18% (974/5442) made 1488 calls to the helpline services up to 30 days before their OHCA (Fig. 1).

3.1. Characteristics of the OHCA patients included in the study

The patients included in the study had a median age of 76 years (IQR: 65–84), the majority were male (56%), had basic educational level and low-income (Table 1). They had a high burden of comorbidities such as cardiac, respiratory, and neurological diseases. Additionally, more than half of these patients redeemed a prescription for antibiotics within 180 days before OHCA. Most of the cardiac arrests occurred in private locations (79%) and had a high rate of bystander CPR (68%). However, patients were less likely to have an initial shockable rhythm (7%), return of spontaneous circulation (23%) and 30-day survival (8%).

Separately, we examined the characteristics of the patients according to the registered symptoms as shown in Supplementary Table S3. Among patients with breathing problems, prior heart failure (HF) was present in 29% and respiratory diseases in 78% of patients. And, 39% of those with chest pain had history of previous ischemic heart disease (IHD). Within 180 days before the call date, nearly half of patients (54%) with breathing problems were assigned with respiratory-related diagnoses and primarily redeemed prescriptions for antibiotics (65%).

3.2. Registered prodromal symptoms 30 days before OHCA

Of 1488 calls, 23% had no symptoms registered, and this was most frequent among calls to the 1813-Medical Helpline (Fig. 1). Overall, no baseline differences were observed between patients with no registered symptoms compared to those with a registered prodromal symptom, besides a lower drug and alcohol abuse and more diabetic disease among the 158 patients with 343 calls with no registered symptoms (Supplementary Table S4). The main analysis included only 816 patients with registered symptoms in 1145 calls. Some of these patients called more than once, thus assigned with more than one registered prodromal symptom. The most common specific categories were breathing problems (17%) and trauma (17%), followed by CNS/unconsciousness (15%), Fig. 2. Symptoms related to the unspecified category were registered in 33% of patients. This included mostly “unclear problem” (43% of the unspecified) and “complication of the known disease” (19% of the unspecified) (data not shown).

A similar distribution was observed in a major part of registered prodromal symptoms when patients were divided according to sex and age groups (Supplementary Fig. S2). However, chest pain and abdominal/back/urinary-related symptoms were twice more registered among men compared to women. Patients aged <65 years had more psychiatric related symptoms compared to older population. (16% vs 1%).

In addition, 83% (677/816) of 816 patients with registered symptoms had also contacted a GP within 30 days before OHCA. Of those, although no information on the reasons for contact was available, more than half had phoned/emailed and 15% (12.5% of 816) had a face-to-face consultation with their GP (data not shown).

3.3. Patients divided according to time period and call type

When patients were divided according to the time periods of their

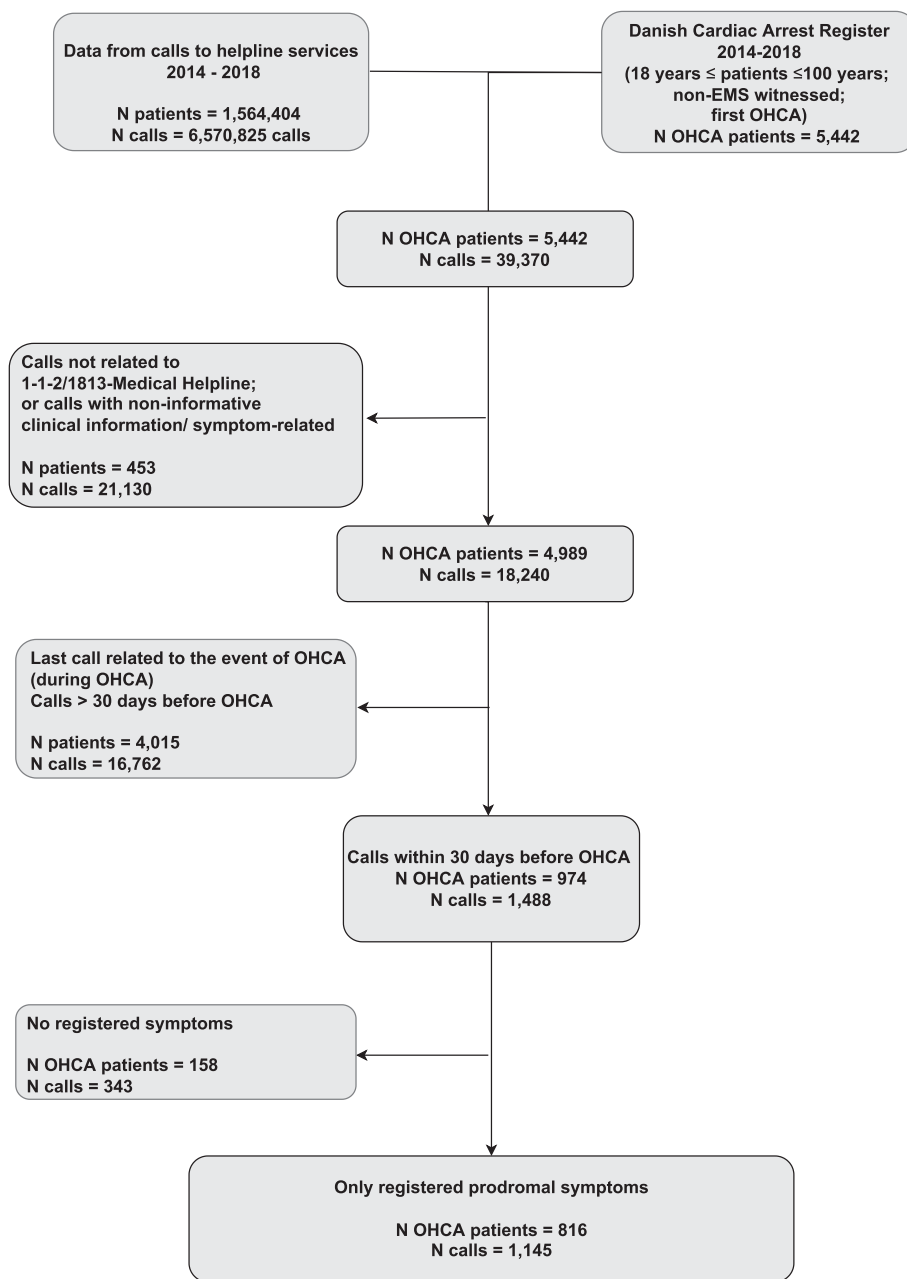


Fig. 1. Flowchart of the study population.

calls (0–7 days and 8–30 days) (Fig. 3a), 41% (471/1145) of calls were made within 0–7 days before OHCA, corresponding to 399 (49%) patients. Among them, besides unspecified (32%), the most frequent categories of registered prodromal symptoms were CNS/unconsciousness (19%), followed by infection/fever (12%) and trauma/exposure (11%). Within 8–30 days before OHCA, breathing problems (21%) and trauma/exposure (20%) remained the most common specific categories, except for the unspecified (33%).

Fig. 3b shows the distribution of the registered prodromal symptoms among patients divided by call type (1–1-2 and 1813-Medical Helpline). Of these, a majority (61%) called the 1813-Medical Helpline, which comprised 59% of all calls, with the most common specific category being abdominal/back/urinary (17%), followed by trauma/exposure (15%), and infection/fever (15%). Patients that called 1–1-2, mainly registered in the categories breathing problems (24%), CNS/unconsciousness (23%), and trauma/exposure (19%). The unspecified category remained the largest with 24% and 39%, respectively for calls to

1–1-2 and 1813-Medical Helpline.

3.4. Multiple calls within 30 days before OHCA

Of all patients, 28% called more than once, where calls to 1813-Medical Helpline outnumbered calls to 1–1-2 (Fig. 4). Characteristics of the patients within each group of calls (“1 call”, “2 calls” and “≥3 calls”) are shown in the Supplementary Table S5. Compared to patients that called less often, patients with ≥3 calls had a median age of 70 years (IQR 54–78), called more within 7 days to OHCA (78%) with mostly registered symptoms related to psychiatric conditions/addiction and mainly had a previous history of psychiatric disorders. They also had a high frequency of hospital discharge diagnoses related to mental and behavioral disorder, redeeming a prescription for antibiotics (63%), antidepressants and antipsychotic drugs (43%) within 180 days before calls.

Table 1
Baseline characteristics of the OHCA population included in the study.

Variables, n (%)	OHCA-patients N = 974
Demographics	
Males	548 (56.3)
Age (years) median (Q1-Q3)	76 [65–84]
Education level *	
Basic education	439 (45.0)
General or vocational upper secondary	355 (36.5)
Bachelor, Master or Doctoral degree	180 (18.5)
Level of income *	
Low	432(44.4)
Medium	405 (41.5)
High	137 (14.1)
Comorbidities within 10 years †	
Cardiac disease	703 (72.2)
Respiratory disease	551 (56.6)
Neurological disease	400 (41.1)
Psychiatric disorders	205 (21.0)
Drug and alcohol abuse	200 (20.5)
Hospital admission/Emergency visit within 180 days before OHCA	363 (37.3)
Medication	
<i>180 days before OHCA</i>	
BB ‡, CCB §, digoxin	411 (42.2)
Antidepressant or antipsychiatric drugs	345 (35.4)
Anticoagulant drugs	197 (20.2)
Antibiotic drugs	533 (54.7)
<i>30 days before OHCA</i>	
QT prolonging drugs	114 (11.7)
Antibiotics	287 (29.5)
Cardiac arrest related factors	
Private location	773 (79.5)
Missing	< 4
Witnessed arrest	462 (47.5)
Missing	< 4
Bystander cardiopulmonary resuscitation	662 (68.2)
Missing	< 4
Bystander defibrillation	27(3.0)
Missing	46 (5.4)
Initial recorded shockable rhythm	68(7.1)
Missing	18
Return of spontaneous circulation (ROSC)	216 (23.2)
Missing	44
Patient has ROSC or has a Glasgow Coma Scale >8 at hospital arrival	184 (20.1)
Missing	60
30-day survival	76 (7.8)

* Missing value (<10) were included in the lower education/income groups.

† Disease categories in hold are represented in the Suppl. Table 2, according to the chapter definition ICD.

‡ BB, beta-blockers drugs; § CCB, Calcium channel blockers.

4. Discussion

In the present study we found that, nearly one out of five patients called the medical helpline services within a month before their cardiac arrest. While the prodromal symptoms registered during these calls varied highly, breathing problems were the most common and nearly twice more common than chest pain. Almost half of the patients called within a week before their OHCA, where CNS/unconsciousness was the most registered specific symptom. More patients called the non-emergency number (1813-Medical Helpline) than the emergency number 1–1-2.

Previously studies have shown that OHCA patients were more likely to be in contact with the healthcare service than the control population, 2 weeks and 1 month before their arrest respectively. [3,5,23] In this study, the main aim was to find symptoms, also considering diagnoses and redeemed prescriptions, that could help identify future OHCA. Our findings suggest that it is difficult to predict future OHCA as the symptoms reported were highly varied. However, breathing problems

might deserve increased attention in the future, as they were commonly registered.

Community-based studies have shown that 33–51% of patients experienced symptoms before their cardiac arrest, with chest pain and dyspnea being the most frequent. [6,7,9,10] The majority of existing studies have been focused on EMS-witnessed cases and examined a short period before OHCA (24 h), where information on symptoms was derived from multiple sources like family at the scene, witnesses, and survivors of the arrest. [6,7,9,10]

By comparison, we excluded EMS-witnessed OHCA, to potentially detect early warnings symptoms. Additionally, we used electronic records of calls, where neither the patients reporting the symptoms, nor the healthcare professional were aware of a future OHCA, thereby avoiding recall bias.

The high occurrence of breathing problems probably reflects (1) the fact that we studied a longer period before the OHCA event, and (2) the different mechanisms of OHCA. Nishiyama et al. also found dyspnea to be more common among EMS-witnessed OHCA – regardless of the etiology of cardiac arrest. [7] In Denmark, one study estimated that difficulty in breathing was the fifth most reported symptom by callers to 1–1-2, and these patients are described as a complex group with severe health problems. [13,24] This is also reflected in our data, where patients with breathing problems had a high number of comorbidities, such as respiratory- and cardiac diseases (especially HF), and within 180 days from calls most had antibiotic prescriptions. The latter could further indicate a deterioration of their chronic pulmonary condition; therefore, reduction of cardiac arrests also requires the investigation and earlier recognition of nonischemic causes of OHCA.

Although coronary heart disease is the leading cause of cardiac arrest, only 9% had chest pain in our cohort. The lower percentage compared to the previous literature could be explained by the high comorbidity burden and increased age among our arrest patients, which increases the likelihood of patients presenting myocardial infarction without chest pain. [25] Concerning this, previously it has been described that predictors of symptoms other than chest pain were older age and female sex, [25,26] as women often experienced fewer chest pain symptoms compared to men. [25,27] In our study, despite the overall frequency of the symptom distribution according to age and sex was similar, chest pain symptoms were twice more registered among men compared to women.

Presyncope/syncope has been described especially among young OHCA patients, [28] and in patients with hypertrophic cardiomyopathy, where unexplained syncope was a risk factor for sudden death. [29] In our study, the high frequency of CNS/unconsciousness-related symptoms (especially among elderly) the week before OHCA was probably due to their cardiac condition, other comorbidity and medication. Further studies are needed to investigate these patients.

Among the registered symptoms, the unspecified category was the largest, as it contains a diversity of registered symptoms not included in the other categories. It has been suggested that symptoms presented before cardiac arrest may be non-specific and therefore considered “unharmful”. [8,30] Studies have shown that people with unstable angina or acute myocardial infarction fail to recognize the warning signs before their ischemic cardiac-related event. [31] In our study, most patients within the unspecified category called the non-emergency number, suggesting that the patient likely has perceived the symptom/condition as less urgent, or difficult to define hence not calling the emergency number instead. “Unclear problems” was the largest part of the unspecified category, its characteristics has been described elsewhere. [32] The presence of non-specific complaints also underline the difficulty for healthcare professionals to perceive a life-threatening symptom/condition. On the other hand, 12.5% of all OHCA patients that called within 30 days also had a face-to-face visit with their GPs. Altogether it reflects that identifying patients presenting symptoms before their OHCA remains challenging.

Lastly, nearly a quarter of patients called more than once, especially

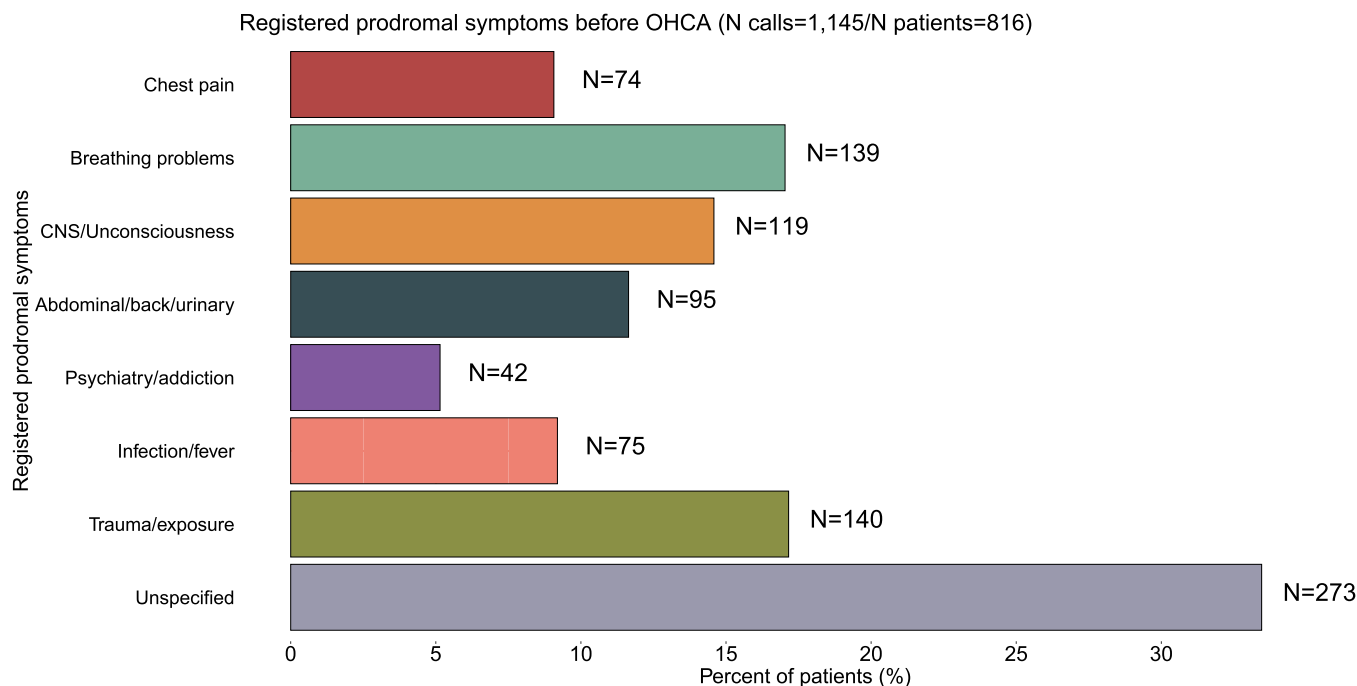


Fig. 2. Overview of prodromal symptoms among patients that called the medical helpline within 30 days before OHCA.

to the non-emergency number and with symptoms related to psychiatric conditions/addiction. Although psychiatric patients are known to be at risk of OHCA, [33] identifying these patients before a cardiac arrest is difficult.

4.1. Clinical implications

Although coronary artery disease remains the predominant cause of cardiac arrest, notably, only one-third (32%) of our OHCA-population had registered the typical classical symptoms (chest pain, breathing problems, and CNS/unconsciousness). Thus, it is important for the healthcare professionals to be aware that patients at risk of OHCA might not always present the “classical symptoms”. Our results suggest that patients experience very different symptoms before their cardiac arrest, which makes the recognition and the prevention of OHCA very challenging. Further studies investigating patients with breathing symptoms and especially patients with unspecific symptoms are warranted to improve risk stratification among these patients.

4.2. Limitations

The study is observational and has a retrospective nature of data collection. Neither the patient nor the healthcare professional on the phone knew about future OHCA during the phone call, which minimizes the potential for recall and response biases. It is important to consider that we use the most severe registered complaint, referred by patients before OHCA as a proxy for describing prodromal symptoms. A large portion of symptoms was not registered (“no reported symptoms”), which could have included specific symptoms resulting in a shift of the frequencies reported in this study. Yet, no differences were observed between the groups of patients with registered symptoms vs. those that had no registered symptoms. We do not know if patients had several severe symptoms, because of the way symptoms are registered we cannot rule out that the decision priority system used to guide healthcare professionals could influence our results. Finally, our study population is selected as based on calls to the non-emergency and EMS services in the Capital Region.

5. Conclusions

Among patients who called medical helplines services up to 30-days before their OHCA, besides symptoms being highly varied, breathing problems were the largest symptom-specific category. Future studies should investigate subgroups of OHCA within these symptom presentations to understand how to develop future preventive interventions.

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Author contributions

N Zyliftari: Dr. Zyliftari contributed to the conception and design of the study, the data acquisition, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript. Dr. Zyliftari has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

C J Lee: Dr. Lee contributed to the conception and design of the study, the supervision, the data acquisition, the data analysis, the data interpretation, the manuscript drafting, the critical revision of the manuscript and the final approval of the version to be submitted.

F Gnesin, A L Møller, E H A Mills, S G Møller, B Jensen, K B Ringgren, K Kragholm, H C Christensen, S N F Blomberg, H L. Tan, F Folke, L Køber contributed to the data interpretation, the manuscript drafting, the critical revision of the manuscript and the final approval of the version to be submitted.

G Gislason and C Torp-Pedersen contributed to the conception and design of the study, the supervision, the data acquisition, the data analysis, the data interpretation, the manuscript drafting, the critical

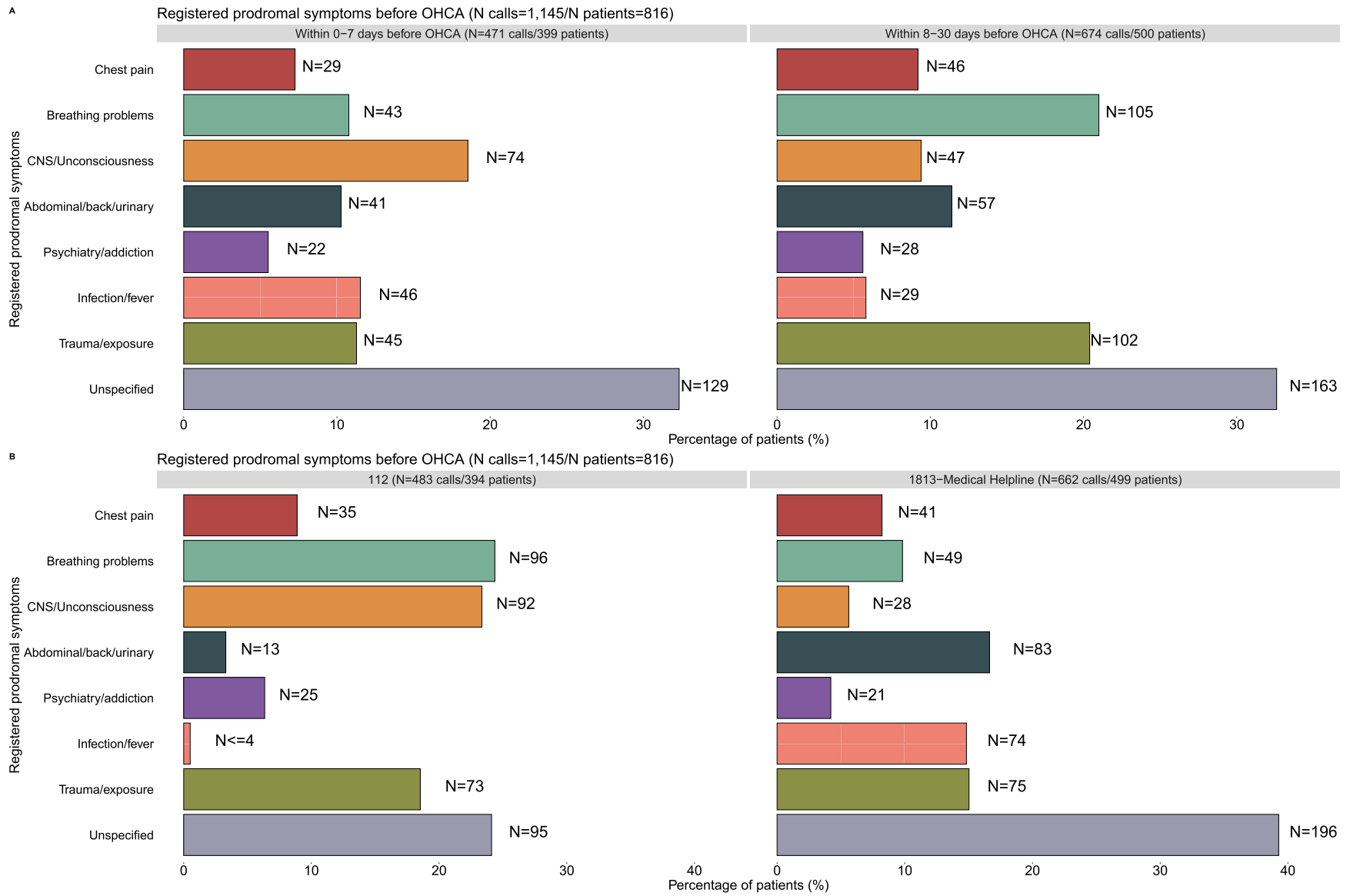


Fig. 3. Prodromal symptoms among patients that called the medical helpline divided by (A) time periods within 0-7 days or 8-30 days before OHCA, ^a and (B) call type, 1-1-2 and 1813-Medical Helpline. ^b

^a (A) Number of calls within 0-7 days before OHCA = 471 (399 patients), number of calls within 8-30 days before OHCA = 674 (500 patients).

^b (B) Number of calls with 1-1-2 = 483 (394 patients), number of calls with 1813-Medical Helpline = 662 (499 patients).

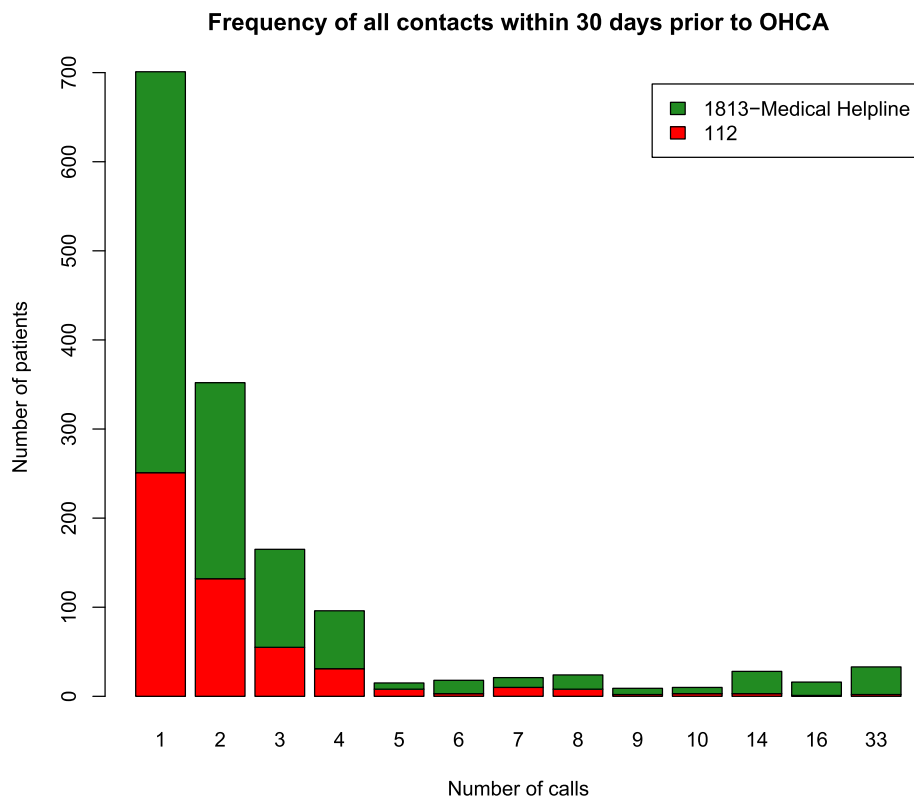


Fig. 4. Frequency of calls within 30 days before OHCA divided by calls to 1813-Medical Helpline (green) and calls to 1–1–2 (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2022.12.004>.

References

- [1] M. Wissenberg, Association of National Initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest, *JAMA* 310 (13) (2013) 1377, <https://doi.org/10.1001/jama.2013.278483>.
- [2] R.J. Myerburg, Sudden cardiac death: exploring the limits of our knowledge, *J. Cardiovasc. Electrophysiol.* 12 (3) (2001) 369–381, <https://doi.org/10.1046/j.1540-8167.2001.00369.x>.
- [3] P. Weeke, Pharmacotherapy and hospital admissions before out-of-hospital cardiac arrest: a nationwide study, *Resuscitation* 81 (12) (2010) 1657–1663, <https://doi.org/10.1016/j.resuscitation.2010.06.025>.
- [4] P. Weeke, Hospital admissions and pharmacotherapy before out-of-hospital cardiac arrest according to age, *Resuscitation* 83 (5) (2012) 584–590, <https://doi.org/10.1016/j.resuscitation.2011.10.024>.
- [5] M. Shuvy, Health care utilization prior to out-of-hospital cardiac arrest: a population-based study, *Resuscitation* 141 (2019) 158–165, <https://doi.org/10.1016/j.resuscitation.2019.04.033>.
- [6] D. Müller, R. Agrawal, H.-R. Arntz, How sudden is sudden cardiac death? *Circulation* 114 (11) (2006) 1146–1150, <https://doi.org/10.1161/CIRCULATIONAHA.106.616318>.
- [7] C. Nishiyama, Prodromal symptoms of out-of-hospital cardiac arrests: a report from a large-scale population-based cohort study, *Resuscitation* 84 (5) (2013) 558–563, <https://doi.org/10.1016/j.resuscitation.2012.10.006>.
- [8] H. Höglund, J.-H. Jansson, A.-S. Forslund, D. Lundblad, Prodromal symptoms and health care consumption prior to out-of-hospital cardiac arrest in patients without previously known ischaemic heart disease, *Resuscitation* 85 (7) (2014) 864–868, <https://doi.org/10.1016/j.resuscitation.2014.03.300>.
- [9] E. Marijon, Warning symptoms are associated with survival from sudden cardiac arrest, *Ann. Intern. Med.* 164 (1) (2016) 23, <https://doi.org/10.7326/M14-2342>.
- [10] S.Y. Lee, K.J. Song, S.D. Shin, K.J. Hong, Epidemiology and outcome of emergency medical service witnessed out-of-hospital-cardiac arrest by prodromal symptom: Nationwide observational study, *Resuscitation* 150 (2020) 50–59, <https://doi.org/10.1016/j.resuscitation.2020.02.042>.
- [11] T.A. Lindskou, The Danish prehospital emergency healthcare system and research possibilities, *Scand. J. Trauma Resusc. Emerg. Med.* 27 (1) (2019) 100, <https://doi.org/10.1186/s13049-019-0676-5>.

- [12] Emergency Medical Services - Healthcare DENMARK [cited 2020 December 8], [Online]. Tilgængelig hos: Available from: <https://www.healthcaredenmark.dk/media/r4fjiqbj/ems.pdf>, 2020.
- [13] M.S. Andersen, S.P. Johnsen, J.N. Sørensen, S.B. Jepsen, J.B. Hansen, E. F. Christensen, Implementing a nationwide criteria-based emergency medical dispatch system: a register-based follow-up study, *Scand. J. Trauma Resusc. Emerg. Med.* 21 (1) (2013) 53, <https://doi.org/10.1186/1757-7241-21-53>.
- [14] M. Schmidt, L. Pedersen, H.T. Sørensen, The Danish civil registration system as a tool in epidemiology, *Eur. J. Epidemiol.* 29 (8) (2014) 541–549, <https://doi.org/10.1007/s10654-014-9930-3>.
- [15] E. Lynge, J.L. Sandegaard, M. Rebolj, The Danish National Patient Register, *Scand. J. Public Health* 39 (7 suppl) (2011) 30–33, <https://doi.org/10.1177/1403494811401482>.
- [16] H. Wallach Kildemoes, H. Toft Sørensen, J. Hallas, The Danish National Prescription Registry, *Scand. J. Public Health* 39 (7 suppl) (2011) 38–41, <https://doi.org/10.1177/1403494810394717>.
- [17] C.B. Pedersen, The Danish civil registration system, *Scand. J. Public Health* 39 (7 suppl) (2011) 22–25, <https://doi.org/10.1177/1403494810387965>.
- [18] K. Helweg-Larsen, The Danish register of causes of death, *Scand. J. Public Health* 39 (7 suppl) (2011) 26–29, <https://doi.org/10.1177/1403494811399958>.
- [19] V.M. Jensen, A.W. Rasmussen, Danish education registers, *Scand. J. Public Health* 39 (7 suppl) (2011) 91–94, <https://doi.org/10.1177/1403494810394715>.
- [20] OECD, Definition and classification of educational programmes: the practical implementation of ISCED 2011, in: *OECD Handbook for Internationally Comparative Education Statistics*, OECD, 2017, pp. 67–76, <https://doi.org/10.1787/9789264279889-8-en>.
- [21] V.J. De Maio, I.G. Stiell, G.A. Wells, D.W. Spaite, Cardiac arrest witnessed by emergency medical services personnel: descriptive epidemiology, prodromal symptoms, and predictors of survival, *Ann. Emerg. Med.* 35 (2) (2000) 138–146, [https://doi.org/10.1016/S0196-0644\(00\)70133-8](https://doi.org/10.1016/S0196-0644(00)70133-8).
- [22] R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2019. <https://www.R-project.org/> (november 2020).
- [23] N. Zylfytari, Contacts with the health care system before out-of-hospital cardiac arrest, *J. Am. Heart Assoc.* 10 (23) (2021), e021827, <https://doi.org/10.1161/JAHA.121.021827>.
- [24] T.A. Lindskou, Symptom, diagnosis and mortality among respiratory emergency medical service patients, *PLoS One* 14 (2) (2019), e0213145, <https://doi.org/10.1371/journal.pone.0213145>.
- [25] E. Puymirat, Clinical outcomes according to symptom presentation in patients with acute myocardial infarction: results from the FAST-MI 2010 registry, *Clin. Cardiol.* 40 (12) (2017) 1256–1263, <https://doi.org/10.1002/clc.22819>.
- [26] T.G. Taylor, Prehospital predictors of atypical STEMI symptoms, *Prehosp. Emerg. Care* (2021) 1–8, <https://doi.org/10.1080/10903127.2021.1987597>.
- [27] G. McKee, M. Mooney, S. O'Donnell, F. O'Brien, M.J. Biddle, D.K. Moser, Multivariate analysis of predictors of pre-hospital delay in acute coronary syndrome, *Int. J. Cardiol.* 168 (3) (2013) 2706–2713, <https://doi.org/10.1016/j.ijcard.2013.03.022>.
- [28] C. Glinge, Symptoms before sudden arrhythmic death syndrome: a Nationwide study among the young in Denmark: symptoms before SADS, *J. Cardiovasc. Electrophysiol.* 26 (7) (2015) 761–767, <https://doi.org/10.1111/jce.12674>.
- [29] P. Spirito, Syncope and risk of sudden death in hypertrophic cardiomyopathy, *Circulation* 119 (13) (2009) 1703–1710, <https://doi.org/10.1161/CIRCULATIONAHA.108.798314>.
- [30] J.C. Lopshire, D.P. Zipes, Sudden cardiac death: better understanding of risks, mechanisms, and treatment, *Circulation* 114 (11) (2006) 1134–1136, <https://doi.org/10.1161/CIRCULATIONAHA.106.647933>.
- [31] S. O'Keefe-McCarthy, L. Ready, Impact of prodromal symptoms on future adverse cardiac-related events: a systematic review, *J. Cardiovasc. Nurs.* 31 (1) (2016) E1–10, <https://doi.org/10.1097/JCN.0000000000000207>.
- [32] S. Otten, The 'unclear problem' category: an analysis of its patient and dispatch characteristics and its trend over time, *BMC Emerg. Med.* 22 (1) (2022) 41, <https://doi.org/10.1186/s12873-022-00597-6>.
- [33] C.A. Barcella, Out-of-hospital cardiac arrest in patients with psychiatric disorders — characteristics and outcomes, *Resuscitation* 143 (2019) 180–188, <https://doi.org/10.1016/j.resuscitation.2019.07.008>.