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Clinical paper

Pulseless electrical activity vs. asystole in adult in-hospital cardiac arrest: Predictors and outcomes

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Abstract

Aim: This observational cohort study aimed to identify factors associated with pulseless electrical activity (PEA) and asystole in in-hospital cardiac arrest (IHCA) patients and to determine whether differences in outcome based on the initial rhythm were explained by patient- and cardiac arrest characteristics.

Methods: Adults with IHCA from 2017 to 2018 were included from the Danish IHCA Registry (DANARREST). Additional data came from population-based registries. Unadjusted (RRs) and adjusted risk ratios (aRRs) were estimated for predictors of initial rhythm, return of spontaneous circulation (ROSC), and survival.

Results: We included 1495 PEA and 1285 asystole patients. The patients did not differ substantially in patient characteristics. Female sex, age>90 years, pulmonary disease, and obesity were associated with initial asystole. Ischemic heart disease and witnessed and monitored cardiac arrest were associated with initial PEA. In unadjusted and adjusted analyses, PEA was associated with increased ROSC (aRR = 1.21, 95% confidence interval [CI] 1.10; 1.33). PEA was also associated with increased 30-day and 1-year survival in the unadjusted analysis, while there was no clear association between the initial rhythm and 30-day (aRR = 0.88, 95% CI 0.71; 1.11) and 1-year (aRR = 0.85, 95% CI 0.69; 1.04) survival when patient- and cardiac arrest characteristics were adjusted for.

Conclusion: In patients with IHCA presenting with PEA or asystole, there were no major differences in patient demographics and comorbidities. The patients differed substantially in cardiac arrest characteristics. Initial PEA was associated with higher risk of ROSC, but there was no difference in 30-day and 1-year survival.

Keywords: In-hospital cardiac arrest, Non-shockable, Initial rhythm, Pulseless electrical activity, Asystole, Predictors, Comorbidities, Cardiac arrest characteristics, Survival

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Introduction

In out-of-hospital cardiac arrest (OHCA) patients, studies have found that increasing age, female sex, prolonged response time, and non-cardiovascular comorbidity and medications are associated with an initial non-shockable rhythm.[1–5] Similar findings have been reported in a recent study on in-hospital cardiac arrest (IHCA) patients,[6] although the topic is less thoroughly investigated in this patient population.

Although patients with a non-shockable rhythm are often grouped together, it has been suggested that PEA and asystole constitute two very different entities with different both pre- and intra-cardiac arrest characteristics.[7–9] PEA is generally associated with better outcomes compared to asystole, and asystole has been suggested to be a "final common pathway" during cardiopulmonary resuscitation.[8,10] Hence, it may be important to distinguish between these two rhythms. Studies looking specifically at individual predictors of PEA and asystole in IHCA patients are scarce.

The aims of the present study were (1) to identify predictors of an initial rhythm of PEA vs. asystole in IHCA patients, and (2) to determine whether possible differences in outcomes based on initial rhythm (PEA vs. asystole) can be explained by differences in patient- and cardiac arrest characteristics.

Methods

Study design, setting, and population

This was an observational cohort study including IHCA patients in Denmark from January 1, 2017 to December 31, 2018. We included adults ($\geq$ 18 years old) with IHCA and an initial non-shockable rhythm. Patients with no linked personal identification number, non-index cardiac arrests within the study period, return of spontaneous circulation (ROSC) before rhythm analysis, and patients with missing data were excluded. The design of the current study largely follows that of a previous study examining shockable vs. non-shockable rhythms.[6]

In Denmark, ethical approval for observational register-based studies is not required.

Data sources

Danish citizens are assigned a unique and permanent personal identification number, which was used to electronically link information from population-based registries to our study population on an individual level.[11,12]

The primary data source was the Danish IHCA Registry (DANARREST) from which data on cardiac arrest characteristics were obtained. Additional information came from the Danish Civil System,[13] the Danish National Patient Registry,[11] and the National Prescription Registry.[14]

Patients with IHCA in the study period were identified through DANARREST, which is an ongoing clinical quality-improvement registry that has collected data on IHCA patients in Denmark since 2017.[15,16] Data on IHCA patients with a clinical indication for CPR (i.e., without a do-not-attempt-cardiopulmonary-resuscitation order) is collected prospectively with the treating physician filling out a case report form immediately after each cardiac arrest. Reporting of data to the registry is mandatory for all Danish hospitals. IHCAs are defined as any cardiac arrest occurring inside the hospital, including the emergency department. Cardiac arrest is defined as unconsciousness, abnormal breathing, and pulselessness as well as initiation of chest compressions and/or defibrillation.

Information on age, sex, and survival was collected from the Danish Civil Registration System, which ensures almost complete follow-up.[13]

The Danish National Patient Registry contains information on all hospitalizations, emergency department contacts, outpatient visits, diagnostic examinations, and surgical procedures in Denmark.[11] From this registry, information on all hospitalizations, cardiac procedures, and diagnoses up to five years before the date of the cardiac arrest was obtained. The five-year timeframe was chosen to secure a reasonable time from the diagnoses to cardiac arrest.[6] Comorbidities were defined using the International Classification of Disease System (ICD-10), using validated codes whenever possible. A complete list of ICD-10 codes, including relevant references, is provided in the Supplement (Table S1).

We obtained information on prescription drugs (by ATC-codes) 180 days prior to the cardiac arrest from the National Prescription Registry, which contains information on all prescriptions dispensed at all Danish pharmacies.[14] The 180-day time-window was chosen to ensure that prescriptions were indicative of active medications only.[6] A complete list of ATC-codes is provided in the Supplement (Table S1).

Outcomes

In the present study, there were different outcomes for the two aims. For the first aim of identifying predictors of initial PEA vs. asystole, the outcome of interest was an initial cardiac arrest rhythm of PEA. For the second aim, the outcomes of interest were ROSC, 30-day survival, and 1-year survival. ROSC was defined as sign of circulation (e.g., palpable pulse) for at least 20 min without the need for chest compressions.[17] If patients were treated with extracorporeal membrane oxygenation, they definitionally had ROSC if they survived to 30 days.

Statistical methods

Continuous variables are presented as medians with quartiles and categorical variables as counts with frequencies.

We used modified Poisson regression models (Poisson distribution and log link function) to obtain risk ratios (RRs) with 95% confidence intervals (CIs).[18] To account for clustering within hospitals, we used generalized estimating equations.

The statistical analyses were divided according to the two study aims. For the first aim, we initially assessed the unadjusted association with the outcome of an initial non-shockable rhythm (PEA/asystole) as the dependent variable and several patient and cardiac arrest characteristics as the independent variable. A RR $>$ 1 thus indicates an association with PEA, whereas a RR $<$ 1 indicates an association with asystole. Afterwards, we created three distinct adjusted models. In model 1, we adjusted for age and sex. In model 2, we subsequently added comorbidities and hospital contacts within the past year. In model 3, we added cardiac arrest characteristics. Complete lists of variables are provided in Table 1 and 2.

Table 1 – Patient characteristics. Categorical data are presented as counts with frequencies (%). Continuous data are presented as medians with quartiles.

	PEA (n = 1495)	Asystole (n = 1285)
Demographics		
Age (years)	74 (65, 81)	75 (66, 82)
Sex		
Male	941 (63)	762 (59)
Female	554 (37)	523 (41)
Hospital contacts within the past year	5 (2, 9)	4 (2, 8)
Comorbidities		
Cardiovascular diseases		
Ischemic heart disease	353 (24)	246 (19)
Heart failure	268 (18)	205 (16)
Arterial hypertension	547 (37)	459 (36)
Pulmonary hypertension	32 (2)	21 (2)
Atrial fibrillation/flutter	327 (22)	301 (23)
Other cardiac dysrhythmias	157 (11)	89 (7)
Valvular heart disease	158 (11)	119 (9)
Aortic disease	55 (4)	42 (3)
Venous thromboembolism	89 (6)	75 (6)
Peripheral vascular disease	162 (11)	153 (12)
Hypercholesterolemia	161 (11)	127 (10)
Neurological diseases		
Cerebrovascular disease	198 (13)	158 (12)
Dementia	38 (3)	41 (3)
Epilepsy	46 (3)	35 (3)
Other[a]	40 (3)	34 (3)
Pulmonary diseases		
Chronic obstructive pulmonary disease	249 (17)	251 (20)
Asthma	46 (3)	53 (4)
Metabolic diseases		
Diabetes mellitus (insulin-dependent)	146 (10)	119 (9)
Diabetes mellitus (non-insulin dependent)	159 (11)	136 (11)
Overweight and obesity	81 (5)	94 (7)
Gastrointestinal diseases		
Peptic ulcer	63 (4)	61 (5)
Liver disease	72 (5)	70 (5)
Pancreatitis	33 (2)	28 (2)
Renal disease	237 (16)	175 (14)
Cancer		
Pulmonary	34 (2)	39 (3)
Breast	29 (2)	21 (2)
Gastrointestinal	51 (3)	66 (5)
Prostate	48 (3)	44 (3)
Hematology	46 (3)	32 (2)
Skin	59 (4)	45 (4)
Other[b]	61 (4)	57 (4)
Psychiatric disorders		
Affective disorder	78 (5)	67 (5)
Schizophrenia and delusional disorder	40 (3)	35 (3)
Alcohol use-related disorder	117 (8)	118 (9)
Other substance use-related disorder	61 (4)	44 (3)

PEA: pulseless electrical activity.
[a] Including Parkinson's disease, hemiplegia, paraplegia, and tetraplegia.
[b] Including, but not limited to, metastatic cancers not classified elsewhere.

Table 2 – Cardiac arrest characteristics. Categorical data are presented as counts with frequencies (%). Continuous data are presented as medians with quartiles.

	PEA (n = 1495)	Asystole (n = 1285)
Witnessed cardiac arrest		
No	204 (14)	498 (39)
Yes	1291 (86)	787 (61)
Monitored cardiac arrest		
No	788 (53)	899 (70)
Yes	707 (47)	386 (30)
Intubation prior to cardiac arrest		
No	1325 (89)	1210 (94)
Yes	170 (11)	75 (6)
Time to rhythm analysis (min)	2 (0, 4)	3 (1, 5)
Time of day		
7–15	598 (40)	415 (32)
15–23	480 (32)	353 (28)
23–7	417 (28)	517 (40)
Weekend		
No	1116 (75)	932 (73)
Yes	379 (25)	353 (27)
Location of cardiac arrest		
Cardiac catherization laboratory	74 (5)	31 (2)
Emergency department	256 (17)	141 (11)
Intensive care unit	187 (13)	88 (7)
Hospital ward	842 (56)	948 (74)
Other[a]	136 (9)	77 (6)

PEA: pulseless electrical activity.
[a] Outpatient clinic or other, operation room, post-anesthesia recovery room.

For the second aim, we repeated the above-mentioned analyses with each outcome (ROSC, 30-day survival, and 1-year survival) as the dependent variable and initial non-shockable rhythm of either PEA or asystole as the independent variable of interest (asystole used as reference group). Cardiac procedures and medications were added to model 2 in addition to the other variables listed for the first aim.

Analyses were conducted in Stata version 16 (StataCorp LP, College Station, TX, USA).

Results

The study included a total of 2780 IHCA patients, including 1495 with initial PEA and 1285 with initial asystole (Fig. 1).

Patient characteristics

The two groups had similar patient demographics. The median age for patients with PEA was 74 years (quartiles: 65, 81 years) and 75 years (quartiles: 66, 82 years) for patients with asystole, and 63% of the PEA population and 59% of the asystole population were male (Table 1).

The two groups were comparable regarding the prevalence of comorbidities and in the number of hospital contacts within the past year prior to the cardiac arrest (Table 1). The largest observed difference was for ischemic heart disease, which was slightly more prevalent in the PEA population (24%) compared to the asystole population (19%).

Cardiac arrest characteristics

The two groups differed substantially in several cardiac arrest characteristics (Table 2). Cardiac arrests with PEA as the presenting rhythm were more often witnessed (86% vs. 61%) and monitored (47% vs. 30%) compared to cardiac arrests with asystole as the presenting rhythm. Patients presenting with PEA were also more often

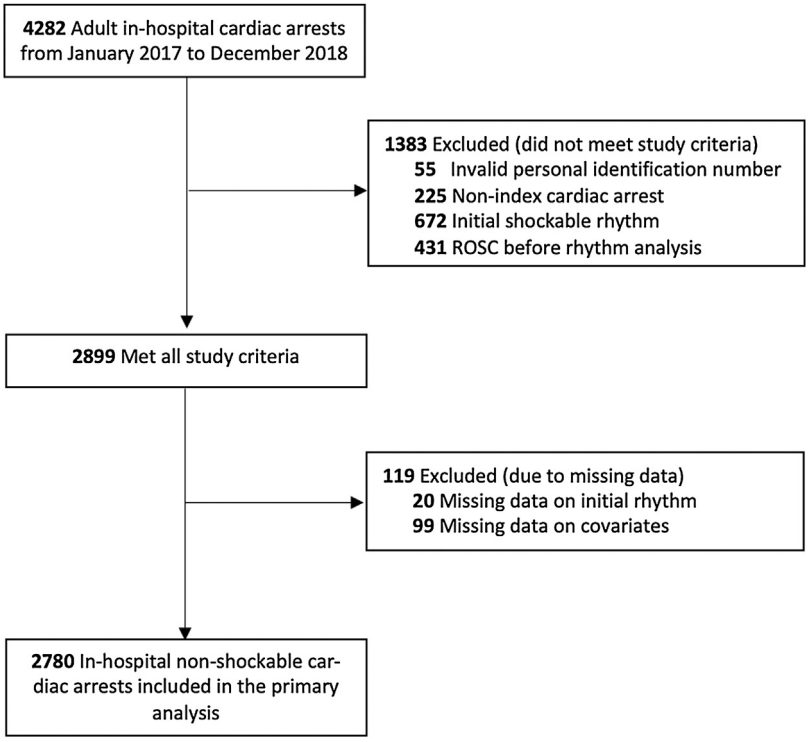

Fig. 1 – Diagram of derivation of the study population.

intubated prior to the cardiac arrest compared to patients presenting with asystole.

The two groups also differed in timing and location of the cardiac arrest. An initial rhythm of asystole was more prevalent during the night, and the location was more often in the hospital ward compared to an initial rhythm of PEA, which in turn was more common in the cardiac catherization laboratory, in the emergency department, and in the intensive care unit (Table 2).

Predictors of initial rhythm

In both the unadjusted and adjusted analyses, age >90 years (as compared to age <50 years old) and female sex were associated with an increased risk of initial asystole (Fig. 2).

There was no association between the majority of comorbidities and initial cardiac arrest rhythm. In the unadjusted and adjusted analyses, pulmonary disease, overweight and obesity, and gastrointestinal cancer were associated with initial asystole, while ischemic heart disease and cardiac dysrhythmias other than atrial fibrillation/flutter were associated with initial PEA (Fig. 2).

Cardiac arrest at night and longer time to rhythm analysis were associated with initial asystole in both unadjusted and adjusted analyses (Fig. 2). Witnessed cardiac arrest, monitored cardiac arrest, and intubation prior to cardiac arrest were all, in both the unadjusted and adjusted analyses, associated with an initial rhythm of PEA.

A full list of RRs with 95% CIs is provided in the Supplement (Table S3).

Outcomes

Outcomes are reported in Table 3. Overall, 48% of the patients in the PEA population had ROSC compared to 33% in the asystole population. Survival to 30 days and to 1 year was 17% and 13% in patients presenting with PEA compared to 15% and 11% in patients presenting with asystole.

In both unadjusted and adjusted analyses, an initial rhythm of PEA was strongly associated with obtaining ROSC compared to an initial rhythm of asystole (Fig. 3). In the unadjusted analyses, an initial rhythm of PEA was also associated with increased risk of survival to 30 days and 1 year. In fully adjusted analyses, when cardiac arrest characteristics were included, asystole as initial rhythm was associated with a higher survival to 30 days and 1 year, however with wide 95% CIs (Fig. 3).

A full list of RRs with 95% CIs is provided in the Supplement (Table S4).

Discussion

The present study of patients with IHCA and an initial non-shockable rhythm had two aims. For the first aim, age >90 years, female sex, cardiac arrest at night, and longer time to rhythm analysis were identified as predictors of initial asystole, whereas witnessed cardiac arrest, monitored cardiac arrest, and intubation prior to cardiac arrest predicted initial PEA. For most comorbidities, no association with an initial rhythm of either PEA or asystole was found. For the second aim, PEA was associated with higher survival compared to asystole in the unadjusted analyses, but the association disappeared when patient- and cardiac arrest characteristics were adjusted for.

Few studies have previously considered PEA and asystole to be two separate rhythms when investigating predictors of initial rhythm and their influence on outcomes in IHCA.[19,20] A recent study of IHCA patients utilizing data from DANARREST investigated predictors of shockable vs. non-shockable rhythm.[21] Higher age, female sex, and

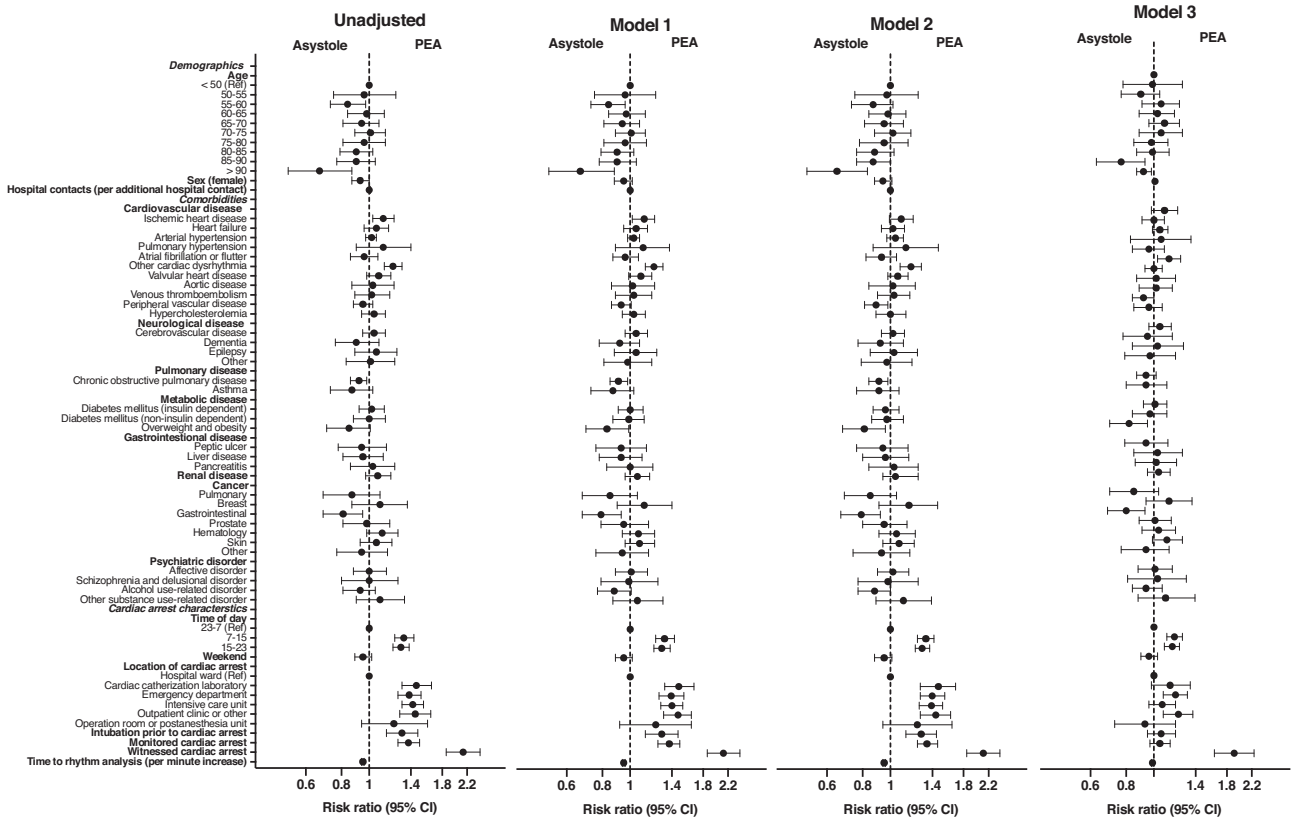

Fig. 2 – Forest plot of risk factors associated with PEA and asystole.
PEA: pulseless electrical activity, CI: confidence interval.
Analyses are presented as risk ratios with 95% confidence intervals. Full list of risk ratios with 95% confidence intervals is provided in the supplement (Table S2). A risk ratio >1 indicates an association with pulseless electrical activity, and a risk ratio <1 indicates an association with asystole.
Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, comorbidities, and hospital contacts within the past year. Model 3: adjusted for age, sex, comorbidities, hospital contacts within the past year, and cardiac arrest characteristics.

specific non-cardiovascular comorbidities such as overweight and obesity were associated with an initial non-shockable rhythm.[21] The present study adds to this knowledge by identifying specific predictors of PEA and asystole, addressing them as two separate initial cardiac arrest rhythms.

In the present study, IHCA patients presenting with PEA or asystole had similar patient demographics, prevalence of most comorbidities, and number of hospital contacts within the past year. Only female sex and age >90 years were associated with asystole in both unadjusted and adjusted analyses (compared to male sex and age <50 years). However, there was no association between other age categories and asystole. These results are consistent with two previous studies on IHCA and OHCA patients, showing no differences in age and sex between patients presenting with PEA or asystole.[22,23] Additional results from studies comparing OHCA patients with PEA or asystole generally report only minor differences in age and sex between the two groups.[18,22,24]

We identified pulmonary disease, overweight and obesity, and gastrointestinal cancer as predictors of initial asystole, while ischemic heart disease and certain cardiac dysrhythmias were associated with an increased risk of PEA. No clear associations were found for the remaining comorbidities or number of hospital contacts within the past year as a surrogate marker of disease severity. It is possible that pulmonary disease[21] and overweight and obesity may result in a higher prevalence of cardiac arrests with a hypoxic cause,[25] which may be linked to asystole as the initial rhythm. Unfortunately, we did not have information on the cause of the cardiac arrest in the present study, and any relationship remains speculative. A study from the United States comparing IHCA patients with PEA or asystole found no clear differences in comorbidities.[23] Previous studies on OHCA

Table 3 – Outcomes. Data are presented as counts with frequencies (%).

	PEA (n = 1495)	Asystole (n = 1285)
ROSC	720 (48)	428 (33)
Survival to 30 days	261 (17)	189 (15)
Survival to 1 year	192 (13)	144 (11)

PEA: pulseless electrical activity, ROSC: return of spontaneous circulation.

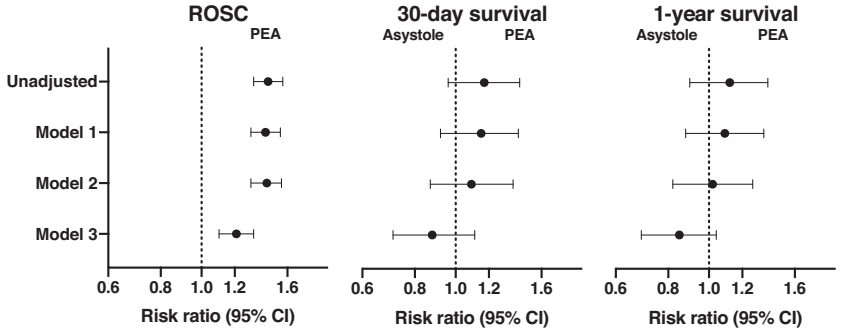

Fig. 3 – Forest plot of outcomes.
ROSC: return of spontaneous circulation, PEA: pulseless electrical activity, CI: confidence interval.
Analyses are presented as risk ratios with 95% confidence intervals. Full list of risk ratios with 95% confidence intervals is provided in the supplement (Table S3). A risk ratio >1 indicates an association between pulseless electrical activity and an improvement in the outcome, and a risk ratio <1 indicates an association between asystole and an improvement in the outcome.
Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, comorbidities, hospital contacts within the past year, cardiac procedures, and medication. Model 3: adjusted for age, sex, comorbidities, hospital contacts within the past year, and cardiac arrest characteristics.

patients also align with the present study and have not found any strong associations regarding cardiovascular and non-cardiovascular disease and PEA vs. asystole either.[8,22] Thus, no data indicates that major differences in the prevalence of cardiovascular and non-cardiovascular comorbidities exist between PEA and asystole cardiac arrest patients.

Previous studies in both OHCA and IHCA populations comparing initial PEA with initial asystole have demonstrated that the two groups primarily differ in relation to cardiac arrest characteristics.[1,8,22–24] This is consistent with findings from the present study. We found that a larger proportion of PEA cardiac arrests were witnessed, monitored, and patients were more often intubated prior to the cardiac arrest. Cardiac arrests with PEA as the initial rhythm also had a shorter time to rhythm analysis and more often occurred during the day or evening and on parts of the hospital with more intensive monitoring (e.g., cardiac catherization laboratory and intensive care unit). When a cardiac arrest is witnessed and/or monitored, the response time and thereby time to CPR and first rhythm analysis is reduced. Intubation prior to the cardiac arrest might be considered a surrogate marker for increased surveillance/monitoring, and this pre-cardiac arrest characteristic may therefore serve as a proxy for shorter time to first rhythm analysis. These findings suggest that initial PEA might partly be a direct consequence of shorter response times due to higher levels of monitoring and more witnessed cardiac arrests. This relates to the notion of asystole being a “final common pathway” during cardiac arrest. Since the present study found that PEA and asystole patients had similar patient demographics, PEA and asystole might represent rhythms within the same spectrum of illness. The common practice of grouping asystole and PEA into non-shockable rhythms may therefore be reasonable in many circumstances but will depend on the research question.

In the literature, there are discrepancies regarding differences in survival between patients presenting with either PEA or asystole. A study by Meaney et al. including IHCA patients from the Unites States found that PEA was associated with higher odds of ROSC but found no difference in survival to hospital discharge between PEA and asystole patients in the adjusted analysis.[23] Additional studies on IHCA patients have not performed adjusted analyses on survival. In absolute numbers one study reported a higher proportion of PEA patients obtaining ROSC and surviving to hospital discharge,[26] while a second study reported a higher proportion of asystole patients surviving longer than hospital discharge.[25] Several studies on OHCA patients have demonstrated comparable short- and long-term survival rates between PEA and asystole patients.[8,22,24,27] In the present study, we found that PEA was associated with ROSC, 30-day survival, and 1-year survival in the unadjusted analyses. The difference in long-term survival (30-day and 1-year) between the two groups disappeared when cardiac arrest characteristics were included in the model. This finding is possibly explained by the higher prevalence of favourable intra-cardiac arrest factors for PEA cardiac arrests, which are associated with increased survival (e.g., higher proportion of witnessed and monitored cardiac arrests).[28–30] These findings suggest that the absolute differences in survival between IHCA patients presenting with PEA or asystole might entirely be explained by differences in circumstances related to the cardiac arrest and not by the first analysed rhythm per se.

Limitations

The results should be interpreted in the context of the following limitations. First, although we used validated codes whenever possible, there is inevitably some uncertainty regarding the use of some of the ICD-10 codes to identify comorbidities, which could introduce misclassification. The use of ICD-10 codes also limited our ability to perform granular severity assessment of the included comorbidities and thereby to adjust for disease severity in the analyses. Second, as we did not have information related to the cause of the cardiac arrest, we were unable to link the individual rhythms to specific causes beyond taking comorbidities into account. Third, we did not have information on reason for hospital admission and were therefore unable to adjust for this potential confounder in the analyses. Fourth, as we did not have data on neurological outcome, we were not

able to compare proportions with good neurological outcome between the two patient groups. Finally, we did not have data on rhythm transitions during the cardiopulmonary resuscitation in the present study, but only focused on the initial recorded rhythm.

Conclusion

In IHCA patients presenting with PEA or asystole, there were no major differences in patient demographics and comorbidities. The two populations primarily differed in cardiac arrest characteristics. Compared to asystole, initial PEA was associated with higher risk of ROSC in all analyses, but the difference in long-term survival disappeared when patient- and cardiac arrest characteristics were adjusted for. Hence, differences in long-term survival between these two populations are explained by differences in cardiac arrest characteristics and not by the first analysed rhythm per se.

Conflicts of interest

None.

CRediT authorship contribution statement

Maria Høybye: Conceptualization, Methodology, Investigation, Writing - original draft, Visualization. **Nikola Stankovic:** Methodology, Writing - review & editing. **Kasper G. Lauridsen:** Conceptualization, Writing - review & editing. **Mathias J. Holmberg:** Methodology, Software, Formal analysis, Investigation, Data curation, Writing - review & editing. **Lars W. Andersen:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision. **Asger Granfeldt:** Conceptualization, Methodology, Investigation, Validation, Writing - review & editing, Supervision, Project administration.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2021.05.036.

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