IJC Heart & Vasculature 41 (2022) 101059

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Outcome after out-of-hospital cardiac arrest in patients with ischaemic and non-ischaemic heart disease: A Danish tertiary-center cohort study

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ARTICLE INFO

Keywords:
Sudden cardiac death
Ischaemic heart disease
Cardiac arrest
Out-of-hospital cardiac arrest
Return to work

ABSTRACT

Background: Mortality following out-of-hospital cardiac arrest (OHCA) is high, and studies on return to work show varying results. It remains uncertain whether mortality and return to work differs between patients with ischaemic heart disease (IHD) and non-ischaemic heart disease (non-IHD).
Aim: To investigate all-cause mortality, cardiac death, and return to work among patients admitted after OHCA with IHD and non-IHD.
Methods: We included 234 consecutive patients admitted to Aarhus University Hospital with OHCA, who were not declared dead in the prehospital setting or upon arrival. Patients were divided into an IHD and a non-IHD group based on history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or signs of obstructive IHD on the admission coronary angiography. Outcome in terms of all-cause mortality, cardiac death, and return to work was evaluated.
Results: All-cause mortality after one month, one year, and five years was 41.9%, 49.1%, and 54.3%. There was no difference in all-cause mortality or cardiac death between IHD and non-IHD patients (all-cause mortality: adjusted HR 0.78, 95% CI, 0.53–1.14; P = 0.19) and cardiac death: adjusted HR 0.93, 95% CI, 0.60–1.43; P = 0.73). Among patients working prior to OHCA the cumulative incidence of patients returning to work was 62.3% after five years with no statistically significant difference between groups.
Conclusion: A favourable outcome was observed in patients admitted after OHCA with a non-significant trend toward a higher mortality in non-IHD patients, possibly indicating that IHD is a favourable cause of cardiac arrest.

1. Introduction

Ischaemic heart disease (IHD) is the predominant cause of cardiac arrest [1,2], whereas inherited cardiac diseases account for a smaller proportion [1,2]. Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality worldwide [3]. OHCA with attempted cardiopulmonary resuscitation is defined as a loss of mechanical cardiac function and the absence of systemic circulation occurring outside of a hospital setting [3]. Mortality following OHCA remains high. An overall one-year mortality of OHCA patients who underwent cardiopulmonary resuscitation has been estimated to be 90.8% [4], while five-year mortality among discharged patients with OHCA has been reported to range between 13% and 43% depending on the underlying comorbidity [5]. The proportion of patients returning to work varies significantly between studies [6–10]. Whether there is a difference between patients with IHD and patients with non-IHD regarding long-term clinical outcome and return to work after OHCA is unknown. The aim of this study was to compare all-cause mortality, cardiac death, and return to work after OHCA between IHD and non-IHD patients.

2. Methods

2.1. Study participants and study design

Patients with OHCA were consecutively enrolled in the study at admission at the Department of Cardiology at Aarhus University

Abbreviations: IHD, Ischaemic heart disease; OHCA, Out-of-hospital cardiac arrest; ROSC, Return of spontaneous circulation.

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https://doi.org/10.1016/j.ijcha.2022.101059
Received 1 April 2022; Received in revised form 11 May 2022; Accepted 16 May 2022

Hospital from 1st of January 2014 until 1st of February 2015. We included patients admitted after OHCA including patients with return of spontaneous circulation (ROSC) prior to admission. Patients who had been declared dead in the prehospital setting were excluded from the study. Patients were also excluded if an invasive coronary angiography was not performed prior to death (i.e. the presence/absence of IHD could not be confirmed prior to death). Patients were also excluded if they had prior implantable cardioverter defibrillator implantations, in case of missing data, and if they were non-Danish residents. Patients were followed from the day of admission until migration, death, or end of follow-up on 3rd of September 2021.

2.2. Data collection

Upon admission, patients underwent invasive coronary angiography if clinically relevant, and coronary revascularization was performed as clinically indicated. Patients were categorized into an IHD and a non-IHD group. Patients with a history of prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery were categorized as IHD patients. Patients were also categorized as IHD patients if the invasive coronary angiography upon admission showed signs of obstructive IHD, as defined by the invasive cardiologist on call. Patients with no history of IHD and no obstructive IHD on the admission coronary angiography were categorized as non-IHD patients (Fig. 1 in the Supplementary Material). Data on baseline characteristics were collected from medical records, including comorbidities, medication use, weight, smoking status, and family history. Causes of OHCA were determined by clinical examinations, imaging modalities, blood analysis, genetic testing, and post mortem examination. An overview of patients receiving psychiatric medication was also included since these patients may have an increased risk of drug-induced QT prolongation and arrhythmias. Family history included sudden cardiac death, survived cardiac arrest, cardiomyopathy, and heart failure in 1st degree relatives. The initial arrest rhythm was categorized as "ventricular tachycardia/ventricular fibrillation", "asystole/pulseless electrical activity" or "unknown" based on the description in the medical records. Information on in-hospital procedures was collected from medical records.

2.3. Data extraction from registries and databases

Each Danish citizen is assigned a unique Civil Personal Register (CPR) number at either birth or when gaining citizenship in Denmark. The CPR number is linked to several health registers and databases making it possible to link and track study participants over a period of time, while also accounting for follow up loss due to death or emigration [11]. From the Danish Civil Registration System [12] we obtained information on vital status and emigration from inclusion and until the day of data extraction on 3rd of September 2021. Cause, manner, and date of death was obtained from the Danish Register of Causes of Death [13]. The Danish National Patient Registry (DNPR) contains information on all diagnoses given and surgical procedures performed on all patients admitted in Danish hospitals since 1977 using The World Health Organization's (WHO's) *International Classification of Diseases Eighth and Tenth Revision* (ICD-8 and ICD-10) [14]. For this study, data on comorbidity within a time period of five years prior to OHCA and until admission were extracted from the DNPR.

The DREAM database consists of data from the Danish Ministry of Employment, Ministry of Integration, Ministry of Education, all Danish municipalities, and Statistics Denmark. The database includes information on all individuals who have received social benefits or other transfer payments since 1991 [15]. Employment status and transfer payments prior to and after the OHCA for all patients were collected from the DREAM database.

2.4. Comorbidities

Comorbidity was measured using the modified Charlson Comorbidity Index by Quan from 2011 [16–18]. The Charlson Comorbidity Index was calculated at baseline using WHO's ICD-10 codes with diagnoses obtained up to five years prior to baseline. Table 1 in the Supplementary Material shows the diagnosis codes used to calculate the Charlson Comorbidity Index.

2.5. Working status

Employment status four weeks prior to the OHCA was assessed. Patients were classified as "working" if they did not receive any social benefits, paid sick leave, or unemployment benefits for four consecutive weeks before OHCA, whereas the remaining patients were categorized as "not working" prior to the OHCA and excluded from the analysis of return to work. Working patients were followed from the week of OHCA and until death or end of follow up on 3rd of September 2021 Working status after OHCA was categorized as "working", "unemployed/on paid sick leave", "retirement pension", and "dead". After OHCA, patients were classified as "working" if they returned to work and continued working for at least four consecutive weeks.

2.6. Statistical analysis

Baseline characteristics for patients with IHD and non-IHD were compared using a chi-square goodness of fit test, student's *t*-test, and Fisher's exact test as appropriate. Normality of continuous variables was checked using QQ plots and histograms. For patients with IHD and non-IHD the cumulative incidence proportions of all-cause mortality and cardiac death was calculated after one month, one year, and five years of follow-up accounting for non-cardiac death as a competing risk in the analysis of cardiac death. Among patients working prior to OHCA, the cumulative proportion of patients who returned to work was calculated at one month, one year, and five years, accounting for death and retirement pension as competing risks. Cox proportional regression analysis was used for calculating hazard ratios of all-cause mortality, cardiac death, and return to work comparing IHD and non-IHD patients. The proportional-hazards assumptions were checked using log–log plots. Analyses were adjusted for age, sex, and Charlson Comorbidity Index. Crude and adjusted HRs were reported. For all analyses, a P value < 0.05 was considered statistically significant. All data analyses were performed using the STATA software version 16.1 (StataCorp, College Station, TX).

3. Ethics

The study was approved by the Danish Patient Safety Authority (record number 31–1521-353).

4. Results

4.1. Patient characteristics

Of 266 patients admitted with OHCA, 32 patients were excluded, leaving 234 patients in the study (Fig. 2 in the Supplementary Material). Baseline characteristics for IHD and non-IHD patients are shown in Table 1. Patients in the IHD group were significantly older than patients in the non-IHD group (median age 67 years vs. 58 years) and were more often males (82.8% vs. 63.0%). In addition, a significantly larger proportion of IHD patients had ventricular tachycardia or ventricular fibrillation as the initial arrest rhythm and were more likely to take medication for heart disease compared with non-IHD patients. Of the patients with IHD, 76 patients (56.7%) underwent percutaneous coronary intervention, of whom 38 (50%) had ST-elevation myocardial infarction. The remaining 58 patients (43.3%) with IHD had previously

Table 1
Baseline characteristics.

	Ischaemic heart disease patients (n=134)	Non-ischaemic heart disease patients (n=100)	*P* value
Male	111 (82.8)	63 (63.0)	0.001
Age (years)	67 (56-75)	58 (49-67)	<0.001
Previous medical history			
Ischaemic heart disease	51 (38.1)	0 (0.0)	–
Hypertension	46 (34.3)	18 (18.0)	0.27
Diabetes mellitus	27 (20.1)	12 (12.0)	0.10
Hypercholesterolemia	18 (13.4)	9 (9.0)	0.21
Current smoker	33 (24.6)	23 (23.0)	0.78
Currently overweight	9 (6.7)	9 (9.0)	0.52
Cardiac comorbidities	0 (0.0)	5 (5.0)	0.01
– Hypertrophic cardiomyopathy	0 (0.0)	1 (1.0)	0.43
– Dilated cardiomyopathy	0 (0.0)	4 (4.0)	0.03
Charlson Comorbidity Index	0 (0-2)	0 (0-1)	0.06
Family history			
Sudden cardiac death	7 (5.2)	6 (6.0)	0.97
Survived cardiac arrest	3 (2.2)	1 (1.0)	0.64
Cardiomyopathy	0 (0.0)	1 (1.0)	0.43
Heart failure	22 (16.4)	8 (8.0)	0.05
Ongoing medication at the time of OHCA			
Heart medication	88 (65.7)	40 (40.0)	0.04
– Anticoagulant therapy	19 (14.2)	14 (14.0)	0.97
– ACE inhibitors	45 (33.6)	17 (17.0)	0.004
– Antiarrhythmic drugs	54 (40.3)	21 (21.0)	0.002
– Diuretics	32 (23.8)	14 (14.0)	0.06
– Lipid lowering drugs	46 (34.3)	21 (21.0)	0.026
– Platelet aggregation inhibitors	52 (38.8)	8 (8.0)	<0.001
– Nitrates	5 (3.7)	1 (1.0)	0.19
Psychiatric medication	17 (12.7)	13 (13.0)	0.21
Initial rhythm			
Ventricular tachycardia/ ventricular fibrillation	108 (80.6)	63 (63.0)	0.003
Asystole/pulseless electrical activity	23 (17.2)	31 (31.0)	0.013
Unknown	3 (2.2)	6 (6.0)	0.18
In-hospital procedures			
Coronary angiogram	122 (91.0)	89 (89.0)	0.60
Percutaneous coronary intervention	76 (56.7)	0 (0.0)	<0.001
Coronary artery bypass graft surgery	10 (7.5)	0 (0.0)	0.006
Implantable Cardioverter Defibrillator implantation	38 (28.4)	36 (36.0)	0.21
Pacemaker implantation	3 (2.2)	0 (0.0)	0.26

Data are presented as median (interquartile range) or number (percentage).

known IHD or showed signs of obstructive IHD during the invasive coronary angiography upon admission. Overall, the burden of comorbidities was low in both groups with over 95% of patients having a Charlson Comorbidity Index ranging from zero to five. Five non-IHD patients had hypertrophic or dilated cardiomyopathy as a preexisting cardiac comorbidity. Ventricular arrhythmia with no identified underlying cause was seen in 18 non-IHD patients. Three patients had aortic dissection, five had a pulmonary embolism, and 21 patients had a non-cardiac cause (e.g. bleeding, severe infection). For the remaining 42 patients the cause of OHCA was not determined. Of the 42 patients, 30 patients (71.4%) had ventricular tachycardia or ventricular fibrillation as the initial arrest rhythm. Of the 30 patients, 12 patients were below 50 years old, of whom six patients underwent genetic testing.

4.2. All-cause mortality

In the overall population, all-cause mortality after one month, one year, and five years were 41.9%, 49.1%, and 54.3%, respectively. There was no difference in all-cause mortality between IHD patients and non-IHD patients (Table 2 and Fig. 1) (adjusted HR: 0.78, 95% CI, 0.53–1.14; $P = 0.19$ for IHD vs. non-IHD patients). Advanced age and Charlson Comorbidity Index were significantly associated with all-cause mortality (adjusted HR: 1.02, 95% CI, 1.01–1.04 per year; $P = 0.002$, and adjusted HR: 1.16, 95% CI, 1.05–1.28 per CCI unit; $P = 0.004$).

4.3. Cardiac death

The cumulative incidence of cardiac death was 33.8%, 39.3%, and 41.5% after one month, one year, and five years, respectively, with no significant differences in risk between IHD patients and non-IHD patients (adjusted HR: 0.93, 95% CI, 0.60–1.43; $P = 0.73$). (Table 2 and Fig. 1). In adjusted analyses, advanced age and female sex were associated with cardiac death (adjusted HR: 1.03, 95% CI, 1.01–1.05 per year; $P < 0.001$, and adjusted HR: 1.61, 95% CI, 1.03–2.51; $P = 0.04$). Thirty patients died due to a non-cardiac cause, registered as respiratory diseases (n = 7), liver and kidney diseases (n = 7), cancer (n = 6), neurologic and neurodegenerative diseases (n = 3), diabetes (n = 3), accidental deaths (n = 2), connective tissue disorders (n = 1), or unspecified cause of death (n = 1). The majority of non-cardiac deaths were observed within one month from study inclusion.

4.4. Return to work

Sixty-one patients were categorized as "working" one month before OHCA. The cumulative incidence of return to work was 9.8%, 44.3%, and 62.3% after one month, one year, and five years (Table 2 and Fig. 2). The overall median time to return to work was 5.8 months (IQR: 9–59 months). Within six months, 15.8% of patients working before OHCA discontinued working, however, 84.2% of patients continued working more than six months, 71% of patients continued working more than one year, and 39.5% continued working more than five years. There was no difference in time to return to work between patients with IHD and with non-IHD (adjusted HR: 0.83, 95% CI, 0.42–1.64; $P = 0.59$ for IHD vs. non-IHD patients) (Table 2).

5. Discussion

In this study we examined all-cause mortality, cardiac death, and return to work in IHD and non-IHD patients with OCHA. We found all-cause mortality and cardiac mortality to be relatively low in comparison with prior reports. Among surviving patients working prior to the OHCA, almost half had returned to work within the first year. Neither all-cause mortality, cardiac death nor return to work differed significantly between IHD and non-IHD patients, but there was a non-significant trend towards a lower mortality in IHD patients which may suggest that IHD is a favourable cause of cardiac arrest compared with other causes.

To our knowledge, the present study is the first to compare all-cause mortality and return to work between patients with IHD and non-IHD. It has been shown that IHD patients are older and are often treated with percutaneous coronary intervention or coronary artery bypass graft surgery when they are admitted with OHCA compared with non-IHD patients [3]. Therefore, it is rather surprising to note that mortality was not higher among IHD patients than non-IHD patients.

Our study showed a lower all-cause mortality and thus higher survival compared with previous studies. In a meta-analysis, 88.3% of patients admitted to the hospital died before hospital discharge [4]. Other studies find varying mortality rates, which largely depends upon time of inclusion in the studies. A meta-analysis has shown a one-year mortality of 90.8% [4], while another study included only OHCA patients who

Table 2
Cumulative incidence proportions and hazard ratios of all-cause mortality, cardiac death, and return to work between patients with ischaemic heart disease and patients with non-ischaemic heart disease.

	1 month		1 year		5 years		Hazard Ratio (crude) (95% CI)	*P* value	Hazard Ratio (adjusted)* (95% CI)	*P* value
	No. of events	Cumulative Incidence (95% CI)	No. of events	Cumulative Incidence (95% CI)	Total no. of events	Cumulative Incidence (95% CI)				
All-cause mortality										
Overall	99	41.9% (35.5–48.1%)	115	49.1% (42.6–5.4%)	127	54.3% (47.7–60.4%)				
Ischaemic heart disease patients	46	38.8% (30.6–46.9%)	53	45.5% (36.9–53.7%)	61	51.5% (42.7–59.6%)	0.82 (0.58–1.17)	0.28	0.78 (0.53–1.14)	0.19
Non-ischaemic heart disease patients	53	46.0% (36.0–55.4%)	62	54.0% (43.8–63.2%)	66	58.0% (47.7–67.0%)	Ref.		Ref.	
Cardiac death										
Overall	80	33.8% (27.8–39.8%)	92	39.3% (33.1–45.5%)	97	41.5% (35.1–47.7%)				
Ischaemic heart disease patients	41	34.3% (26.4–42.4%)	48	41.0% (32.7–49.2%)	51	43.3% (34.8–51.5%)	1.03 (0.69–1.55)	0.87	0.93 (0.60–1.43)	0.73
Non-ischaemic heart disease patients	39	33.0% (24.0–42.2%)	44	37.0% (27.6%–46.4%)	46	39.0% (29.5–48.4%)	Ref.		Ref.	
Return to work										
Overall	6	9.8% (4.0–18.8%)	27	44.3% (31.6–56.1%)	38	62.3% (48.9–73.1%)				
Ischaemic heart disease patients	1	3.0% (0.2–13.4%)	13	39.4% (23.1–55.4%)	21	63.6% (44.9–77.5%)	0.98 (0.52–1.86)	0.96	0.83 (0.42–1.64)	0.59
Non-ischaemic heart disease patients	5	17.9% (6.5–33.7%)	14	50.0% (30.6–66.6%)	17	60.7% (40.4–76.0%)	Ref.		Ref.	

*Adjusted for age, sex, and Charlson comorbidity index.

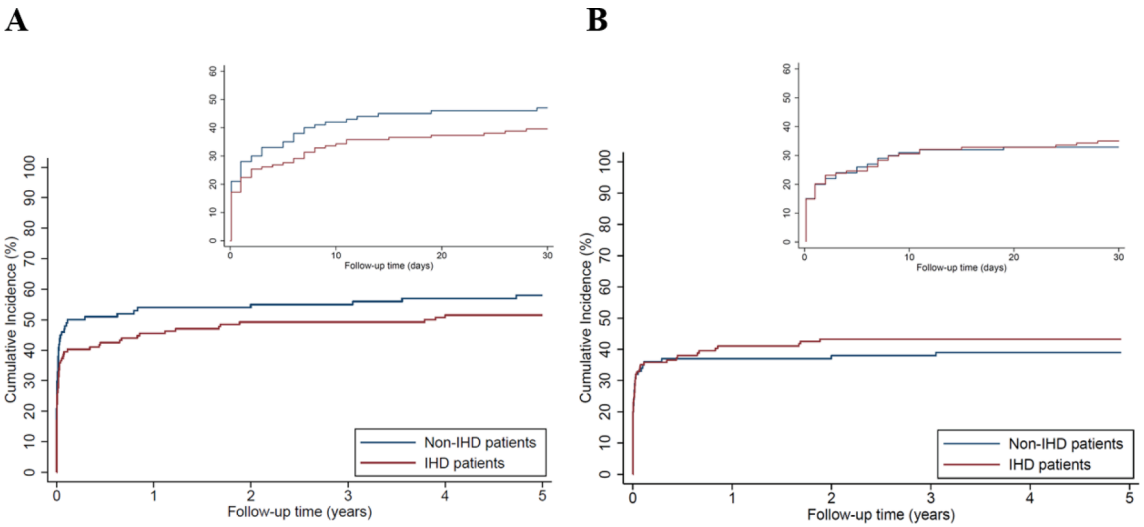

Fig. 1. Cumulative incidence of (A) all-cause mortality and (B) cardiac death in patients with ischaemic heart disease (IHD) and patients with non-ischaemic heart disease (non-IHD).

survived to be discharged [5]. The authors found a five-year mortality among discharged patients ranging between 13% and 43% depending on underlying comorbidities [5]. We excluded patients admitted after OHCA who were declared dead prior to admission or upon arrival which likely contributed to a higher survival compared to other studies. We also found that 81% of IHD patients and 63% of non-IHD patients had an initial shockable rhythm, likely resulting in a higher survival than the total OHCA cohort. Factors positively associated with survival such as shorter emergency medical service response time and availability of bystander cardiopulmonary resuscitation were unknown in our study, but may have resulted in lower mortality rates compared to existing literature [19,20]. Procedures such as percutaneous coronary intervention was available to all eligible patients in our study, which has shown to be significantly associated with a reduced short and long-term mortality [21]. In Denmark, a well-established nationwide prehospital setup using an emergency telephone number and ambulances equipped with basic life support equipment and a defibrillator, as well as the use of helicopter emergency medical service has been implemented. Patients with OHCA are assessed with prehospital electrocardiogram and can be triaged directly to an invasive heart centre for percutaneous coronary

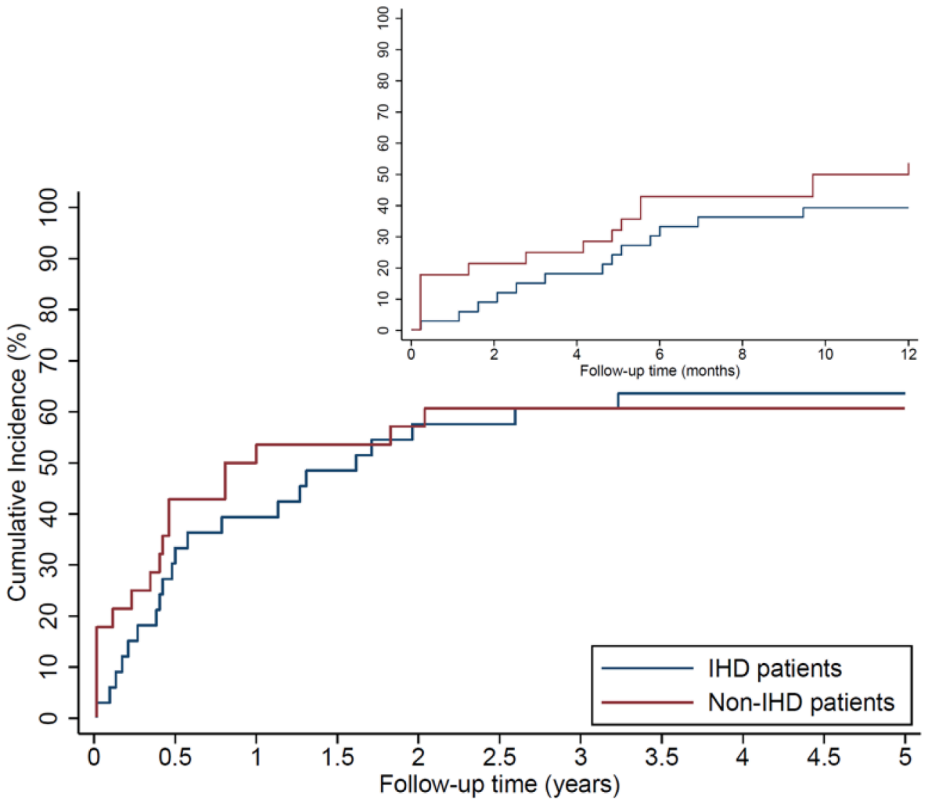

Fig. 2. Cumulative incidence of time to return to work in patients with ischaemic heart disease (IHD) and patients with non-ischaemic heart disease (non-IHD).

intervention. This has shown an improved survival in OHCA patients [22]. Among other factors, a selected cohort with admission to a highly specialised cardiology department and access to highly specialised treatments such as cardiopulmonary support, extracorporeal membrane oxygenation, percutaneous coronary intervention, and coronary artery bypass graft surgery in our study may partly explain the lower overall mortality rates compared to other studies. We saw a minor non-significant trend toward a higher all-cause mortality in non-IHD patients driven by non-cardiac causes, however, there was no difference in cardiac death between IHD and non-IHD patients. The non-IHD group was very heterogeneous, and the majority of non-cardiac deaths occurred within one month after OHCA and may have been the cause of cardiac arrest.

In our study, most working patients returned to work within five years. Existing literature examining return to work after OHCA suggests that the majority of survivors return to work with incidences ranging between 62.8% and 76.6% within one and five years [6,8,10]. In line with existing literature, we report the majority of survivors returning to work after OHCA with an overall return to work of 62.3% after five years. The degree of competing comorbidities in our population was low and therefore the study provides a relatively pure estimate of the effect of OHCA on return to work. A study by Kragholm et al reported an overall return to work rate of 76.6% after five years in 30-day survivors [6]. They report a larger proportion of patients working prior to cardiac arrest and the median age was lower, possibly explaining the higher rate of return to work. Median time of return to work was almost 6 months in our study, which is in accordance with previously reported median return to work times of 4 and 8 months after OHCA [6,10]. In our study, 71% of patients continued working for more than one year, and 39.5% of patients continued working more than five years. The decrease in patients continuing working for more than one year vs. working for more than five years could be explained by patients approaching the retirement age.

The strengths of this study include the complete follow-up on all patients with data from medical records and well-validated registries [23]. However, our study has limitations. First, the number of patients was relatively small; in particular in the return to work analysis because a significant proportion of patients had retired prior to OHCA. This causes relatively widened confidence intervals and reduces the statistical power in the comparison of IHD and non-IHD patients. Second, even though patients classified as return to work after OHCA were followed from the initial event of return to work and up until receiving social benefits, paid sick leave, or unemployment benefits, future return to work was not taken into account. It has been shown that patients with coronary heart disease undergoing percutaneous coronary intervention who return to work have recurrent sick leaves, and therefore the event of returning to work may not indicate a full recovery [24]. A reduction in hours could reflect an impaired ability to work full hours, which we did not account for. Third, patients classified as "working" prior to OHCA and "returning to work" after OHCA if they did not receive benefits were assumed to be working. Some patients not working and not receiving benefits may have been economically funded by their spouses, resulting in misclassification of the outcome. However, this figure is probably low as it has been estimated that around 2% of the Danish population between 40 and 67 years are without personal income [24].

6. Conclusion

In patients admitted with OHCA, and not declared dead upon arrival, the overall prognosis was favourable with approximately 50% of patients alive after five years. Cardiac death was the predominant cause of death. Most working patients returned to work within five years with a median time until return to work of six months. There was no statistically significant difference in all-cause mortality, cardiac death, and return to work between patients with IHD and patients with non-IHD, but a trend toward a higher mortality in patients with non-IHD driven by non-cardiac causes was found, which may indicate that IHD is a favourable cause of cardiac arrest.

Data availability

Data will not be made available due to Danish legislation.

Sources of funding

The project was funded by the Novo Nordisk Foundation (NNF18OC0031258). The Novo Nordisk Foundation had no involvement in the design or conduct of the study.

CRediT authorship contribution statement

Marie-Louise Beier Guldfeldt: Formal analysis, Investigation, Data curation, Writing – original draft. **Tanja Charlotte Frederiksen:** Conceptualization, Methodology, Writing – review & editing. **Anders Krogh Broendberg:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing. **Morten Krogh Christiansen:** Conceptualization, Methodology, Writing – review & editing. **Henrik Kjaerulf Jensen:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

H.K. Jensen is supported by the Novo Nordisk Foundation (NNF18OC0031258). The other 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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101059.

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