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Higher 1-year mortality in women admitted to intensive care units after cardiac arrest: A nationwide overview from the Netherlands between 2010 and 2018

Loes Mandigers [a], Fabian Termorshuizen [b,c], Nicolette F. de Keizer [b,c], Wim Rietdijk [d,*], Diederik Gommers [a], Dinis dos Reis Miranda [a], Corstiaan A. den Uil [a,e]

[a] Department of Intensive Care, Erasmus University Medical Center, Rotterdam, the Netherlands
[b] National Intensive Care Evaluation (NICE) foundation, Amsterdam, the Netherlands
[c] Department of Medical Informatics, Amsterdam UMC, Amsterdam Public Health Research Institute, University of Amsterdam, Amsterdam, the Netherlands
[d] Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, the Netherlands
[e] Department of Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Purpose: We study sex differences in 1-year mortality of out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) patients admitted to the intensive care unit (ICU).
Data: A retrospective cohort analysis of OHCA and IHCA patients registered in the NICE registry in the Netherlands. The primary and secondary outcomes were 1-year and hospital mortality, respectively.
Results: We included 19,440 OHCA patients (5977 women, 30.7%) and 13,461 IHCA patients (4889 women, 36.3%). For OHCA, 1-year mortality was 63.9% in women and 52.6% in men (Hazard Ratio [HR] 1.28, 95% Confidence Interval [95% CI] 1.23–1.34). For IHCA, 1-year mortality was 60.0% in women and 57.0% in men (HR 1.09, 95% CI 1.04–1.14). In OHCA, hospital mortality was 57.4% in women and 46.5% in men (Odds Ratio [OR] 1.42, 95% CI 1.33–1.52). In IHCA, hospital mortality was 52.0% in women and 48.2% in men (OR 1.11, 95% CI 1.03–1.20).
Conclusion: Women admitted to the ICU after cardiac arrest have a higher mortality rate than men. After left-truncation, we found that this sex difference persisted for OHCA. For IHCA we found that the effect of sex was mainly present in the initial phase after the cardiac arrest.

1. Introduction

Despite the advances in prevention and treatment, cardiovascular diseases (CVDs) are still the number one cause of death worldwide. [1] Globally CVDs account for almost one third of the deaths and in Europe even half of the deaths are caused by CVDs. [1] Within the CVDs cardiac arrest has the highest mortality rate. The mortality rate after cardiac arrest varies between 58 and 61% for patients admitted alive to the hospital. [2,3] Even though there are many epidemiological studies in CVDs as well as in cardiac arrest, there are still many risk factors understudied.

One of the factors that has already been studied in CVDs but less in cardiac arrest is sex. Women with CVDs are older [4,5], have more cardiovascular risk factors [4,6-8], and present more often with atypical symptoms than men. [9] Recently, some studies have also shown the importance of sex differences in patient characteristics, pathophysiology, course, and outcome after cardiac arrest. [4,6-11] Similar to other CVDs, women are older and there is a difference in type and number of comorbidities. [12-21] When cardiac arrest occurs in women, the primary cardiac rhythm is less often shockable and women have a lower number of affected coronary arteries. [12,15,22,23] Women with cardiac arrest have significant higher short-term mortality, however these differences tend to disappear after adjustment for age and primary cardiac rhythm. [13,15,16,18,19,21,24]

A recent study in 5717 emergency medical services (EMS)-treated out of hospital cardiac arrest (OHCA) patients in the Netherlands has shown that women have a lower rate of primary shockable cardiac rhythm and receive bystander cardiopulmonary resuscitation (CPR) less frequently. [12] Women have a higher mortality to hospital discharge than men, however this effect disappeared in the subgroup of patients with primary shockable cardiac rhythms. [12] Therefore, the authors hypothesised that the disparity between women and men may be caused by a longer delay from arrest onset to recognition by bystanders, more rapid transition to non-shockable cardiac rhythms due

* Corresponding author at: Erasmus University Medical Center, Department of Hospital Pharmacy, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
E-mail address: w.rietdijk@erasmusmc.nl (W. Rietdijk).

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to biological factors, or a combination of both. [12] The majority of the studies on sex differences in cardiac arrest are focussing on short-term mortality. However, data presenting longer-term mortality is lacking.

Recent studies, have also examined the mortality of in-hospital cardiac arrest (IHCA) patients in the Netherlands. [25-28] These studies note that there is scarce data available on long-term outcomes (and particularly 1-year mortality) of IHCA patients. [27] Furthermore, Schluep et al. found in their systematic review a 1-year survival of 13.4% in IHCA patients. However, this study included all IHCA patients, also patients that were not admitted to the intensive care unit (ICU). [28] This specific patient group, IHCA patients admitted to the ICU, is still an understudied group of which not much is known.

In order to contribute to existing knowledge on sex differences in outcomes of OHCA and IHCA patients, the purpose of this study was to examine the 1-year mortality of OHCA and IHCA patients admitted to the ICU in the Netherlands. Patients with an OHCA or IHCA who are subsequently admitted to the ICU are an important group to study. Especially as these patients survived the first episode of cardiac arrest (CA) (i.e., CPR). However, they are prone to haemodynamic deterioration/instability, ischaemia/reperfusion injury, and neurological damage [25]. This study is a first step in investigating possible sex differences in long-term mortality after ICU admission for both OHCA and IHCA patients.

2. Materials and methods

2.1. Population, setting, and design

In this retrospective cohort study, we used data that was partly reported in a previous study by our research group. [25] However, we expanded this dataset with two additional years and changed the primary focus of the analysis. Observational data of all ICU admitted patients in the Netherlands are collected in the National Intensive Care Evaluation (NICE) registry. This is a nationwide quality of care registry for ICUs in the Netherlands. In this registry data on demographics, physiological and diagnostic data, patient outcomes, and ICU characteristics are prospectively collected. We performed a retrospective analysis of the data, derived from approximately 85% of the ICU departments in 2010 to 100% of the ICU departments in 2018. [25]

All adult cardiac arrest patients admitted to the ICUs in the Netherlands between January 2010 and December 2018 were included. The Medical Ethics Committee of the Erasmus MC Rotterdam, the Netherlands (number MEC − 2018-1228) and the Scientific Board of the NICE Foundation (number 2018–01) approved this study. The need for informed consent was waived.

2.2. Characteristics and clinical outcomes

The characteristics and clinical outcomes we collected are described before. [25] We included patient characteristics, admission characteristics, and clinical outcomes. In Supplementary Digital Content Table A, we provide a full list of the definitions of these characteristics and clinical outcomes included in the study.

We included all adult (≥18 years) patients registered with an admission diagnosis of CA or CPR. Next, we stratified the characteristics and clinical outcomes for OHCA and IHCA patients. However, OHCA and IHCA were not encoded in the NICE registry. Therefore, we defined OHCA as an admission diagnosis of CA or CPR, with an admission origin in the ED or home. IHCA was defined as an admission diagnosis of CA or CPR, with admission origin within the hospital, excluding the emergency department (ED). [25] The characteristics and outcomes were analysed for OHCA patients and IHCA patients separately. Next, we stratified the data based on sex and compared characteristics and clinical outcomes of women and men.

2.3. Primary and secondary outcomes

For our primary outcome we will focus on 1-year mortality. We choose this as our primary outcome as a previous consensus stated that for large studies long-term outcomes are preferred. [29] In order to determine this primary outcome, 1-year mortality, we linked data from Vektis, an administrative database with claims of all insurance companies in the Netherlands. [30,31] Our secondary outcome is hospital mortality.

2.4. Statistical analysis

Descriptive statistics are reported as number (percentage, %) or median (interquartile range, IQR). To test for differences between women and men, we used Chi-square tests for categorical variables and Wilcoxon tests for continuous variables. To study the primary outcome, 1-year mortality, we performed multivariable Cox proportional hazard regressions comparing women and men, for OHCA and IHCA separately. The proportional hazard assumption in the Cox proportional hazard regressions may be violated as the effect of sex on the hazard of death is different for different intervals since ICU admission. In order to test this, we will repeat the Cox proportional hazard regressions with different left-truncation thresholds (i.e., hospital discharge, 30 days, 90 days, 180 days, and 270 days). The results of the Cox proportional hazard regressions are presented as Hazard Ratios (HR) and 95% confidence interval (95% CI).

To analyse the secondary outcome, hospital mortality, we performed a binary logistic regression comparing women and men for OHCA and IHCA separately. These results are presented as Odds Ratios (OR) and 95% CI. Both the Cox proportional hazard regression as well as the binary logistic regression were adjusted for age, body mass index [BMI], medical history (e.g., renal insufficiency/dialysis, chronic obstructive pulmonary disease [COPD]/ chronic respiratory insufficiency, cardiovascular insufficiency, liver cirrhosis, malignancy [including hematologic malignancies], immunologic insufficiency [including AIDS]), diagnosis on admission (i.e., mechanical ventilation, cerebrovascular accident [CVA], intracranial mass, gastro intestinal bleeding, and diabetes mellitus), and Glasgow Coma Scale (GCS). We included these admission characteristics as these are known at ICU admission and are relevant factors in explaining mortality. All analyses were performed using R-studio, version 3.6.1, and p-values <0.05 were considered statistically significant.

3. Results

Of the total 689,289 patients included in the NICE registry between 2010 and 2018, 34,036 (4.9%) were admitted to the ICU due to CA. In 32,901 patients the location of arrest (OHCA or IHCA) could be determined and they were included in this study. 19,440 (59.1%) patients suffered from an OHCA, of which 5977 (30.8%) were women, and 13,461 (40.9%) patients suffered from an IHCA, of which 4889 (36.3%) were women.

3.1. Descriptive statistics

The descriptive statistics are presented in Table 1 showing the sex differences in patient characteristics and admission characteristics of OHCA patients and Table 2 showing the sex differences in patient characteristics and admission characteristics of IHCA patients. We also provide information about the number of missing values for each variable. As for the GCS at admission and 24 h after ICU admission were measured only in earlier years of the NICE registry. It was decided to stop collection of the GCS data in recent years. For this reason, the number of missing values is in these variables are large. Nevertheless, we decided to present the data that is available but not use GCS in our multivariable analysis.

Table 1
Patient and admission characteristics for OHCA patients, for women and men.

	Total	Women	Men	p-value	Missing values (%)^
Patient characteristics					
Patient no	19,440	5977	13,463		
Age (IQR)	66 (55–75)	67 (54–76)	66 (56–74)	0.07	0 (0.0)
BMI (IQR)	25.8 (23.4–28.7)	25.7 (22.9–29.4)	26.0 (23.7–28.1)	0.03	1294 (6.7%)
History					0 (0.0)
Cardiovascular insufficiency (%)	1297 (6.7)	322 (5.4)	975 (7.2)	<0.01	
COPD/respiratory insufficiency (%)	2731 (14.0)	1000 (16.7)	1731 (12.9)	<0.01	
Renal insufficiency (%)	1011 (5.2)	299 (5.0)	712 (5.3)	0.43	
Liver cirrhosis (%)	173 (0.9)	69 (1.2)	104 (0.8)	0.01	
Malignancy including hematological malignancy (%)	521 (2.7)	196 (3.3)	325 (2.4)	<0.01	
Immunodeficiency (%)	700 (3.6)	285 (4.8)	415 (3.1)	<0.01	
Admission characteristics					
APACHE IV estimated mortality rate (IQR)	0.8 (0.5–0.9)	0.8 (0.5–0.9)	0.8 (0.5–0.9)	1.00	80 (0.04)
Admission type				0.36	80 (0.04)
Medical (%)	19,193 (99.1)	5896 (99.1)	13,297 (99.1)		
Urgent surgical (%)	158 (0.8)	42 (0.7)	116 (0.9)		
Elective surgical (%)	9 (<0.1)	4 (0.1)	5 (<0.1)		
GCS *on admission*				0.08	4836 (25)**
GCS ≤ 5 (%)	10,454 (71.6)	3310 (72.8)	7144 (71.0)		
GCS 6–14 (%)	2260 (15.5)	670 (14.7)	1590 (15.8)		
GCS 15 (%)	1890 (12.9)	564 (12.4)	1326 (13.2)		
Diagnosis on admission					0 (0.0)
Mechanical ventilation (%)	17,711 (91.1)	5404 (90.4)	12,307 (91.4)	0.03	
CVA (%)	568 (2.9)	247 (4.1)	321 (2.4)	<0.01	
Intracranial mass (%)	434 (2.2)	199 (3.3)	235 (1.7)	<0.01	
Gastro intestinal bleeding (%)	291 (1.5)	103 (1.7)	188 (1.4)	0.10	
Diabetes Mellitus (%)	2976 (15.3)	1032 (17.3)	1944 (14.4)	<0.01	
GCS - *At 24 h after ICU admission*				0.02	4864 (25%)**
GCS ≤ 5 (%)	8650 (59.3)	2755 (60.8)	5895 (58.7)		
GCS 6–14 (%)	2492 (17.1)	719 (15.9)	1773 (17.6)		
GCS 15 (%)	3434 (23.6)	1056 (23.3)	2378 (23.7)		
Diagnosis at 24 h of ICU admission					0 (0.0)
AKI (%)	3082 (15.9)	994 (16.6)	2088 (15.5)	0.05	
Mechanical ventilation (%)	18,238 (93.8)	5576 (93.3)	12,662 (94.1)	<0.05	
Infection (%)	1481 (7.6)	520 (8.7)	961 (7.1)	<0.01	
Vasoactive medication (%)	14,526 (74.7)	4371 (73.1)	10,155 (75.4)	<0.01	
Thrombolytic therapy (%)	806 (4.1)	224 (3.7)	582 (4.3)	0.07	
Academic hospital (%)	5405 (27.8)	1576 (26.4)	3829 (28.4)	<0.01	0 (0.0)

OHCA: out-of-hospital cardiac arrest, BMI: body-mass index, COPD: chronic obstructive pulmonary disease, APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Coma Scale, CVA: cerebrovascular accident, AKI: acute kidney injury.
** The Glasgow Coma Scale (GCS) at admission and 24 h after ICU admission were measured only in earlier years of the NICE registry. It was decided to stop collection of the GCS data in recent years. For this reason, the number of missing values is large. Nevertheless, we decided to present the data that is available, but not use it in our multivariable models.
^The missing values for women and men are presented separately in Supplementary Digital Content Table G (OHCA).

In OHCA patients, we found no statistically significant difference in age between women and men (67 years vs. 66 years, $p = 0.07$). Women had a lower incidence of prior cardiovascular insufficiency than men (5.4% vs. 7.2%, $p < 0.01$). A higher incidence of prior COPD/respiratory insufficiency was found in women (16.7%) than in men (12.9%, $p < 0.01$). At admission, women were more often known with diabetes mellitus than men (17.3% vs. 14.4%, $p < 0.01$). Table 3 presents the clinical outcomes. Women had shorter length of ICU stay than men (4.2 days vs.6.2 days, $p < 0.01$).

In IHCA patients, women had a higher median age than men (70 years vs. 68 years, $p < 0.01$). As in OHCA patients, women who suffered IHCA had a lower incidence of prior cardiovascular insufficiency than men (9.1% vs. 11.6%, $p < 0.01$) and a higher incidence of prior COPD/respiratory insufficiency was found in women (18.6%) than in men (16.7%, $p < 0.01$). At admission, women received less often mechanical ventilation than men (85.6% vs. 87.5%, p < 0.01). Women had shorter length of ICU stay (5.3 days vs. 6.4 days, p < 0.01), as shown in Table 3.

3.2. Primary outcome: 1-year mortality

In OHCA, women had a higher 1-year mortality than men (63.9% vs. 52.6%, p < 0.01, Table 3). After adjustment in the Cox proportional hazard regression model this mortality difference remained statistically significant (HR 1.28, 95% CI 1.23–1.34, Table 4). Fig. 1 shows the Kaplan-Meier curve of 1-year mortality in OHCA patients. The Supplementary Digital Content Table B shows that the largest mortality difference between women and men in our study population is present in the initial phase after CA.

In IHCA, women had higher 1-year mortality than men (60.0% vs. 57.0%, $p < 0.01$, Table 3). After adjustment in the Cox proportional hazard regression model this mortality difference remained statistically significant (HR: 1.09, 95% CI 1.04–1.14, Table 4). Fig. 2 shows the Kaplan-Meier curve of 1-year mortality in IHCA patients. Likewise, the largest mortality difference between women and men in our study population is present in the initial phase after the cardiac arrest (4.2%, Supplementary Digital Content Table C).

3.3. Secondary outcome: hospital mortality

In OHCA patients, women had a higher hospital mortality than men (57.4% vs. 46.5%, $p < 0.01$, Table 3). Supplementary Digital Content Table D shows that in the adjusted binary logistic regression model, this difference in hospital mortality remained statistically significant (OR 1.44, 95% CI 1.33–1.52).

In IHCA patients, women had a higher hospital mortality than men (52.0% vs. 48.2%, p < 0.01, Table 3). Supplementary Digital Content Table D shows that in the adjusted logistic regression model, this difference in hospital mortality remained statistically significant (OR 1.11, 95% CI 1.03–1.20).

Table 2
Patient and admission characteristics for IHCA patients, for women and men.

	Total	Women	Men	p-value	Missing values (%)^
Patient characteristics					
Patient no	13,461	4889	8572		
Age (IQR)	69 (59–77)	70 (58–78)	68 (59–76)	<0.01	0 (0.0)
BMI (IQR)	25.8 (23.4–29.1)	25.7 (22.9–29.7)	25.8 (23.5–28.4)	0.94	849 (6%)
History					0 (0.0)
Cardiovascular insufficiency (%)	1438 (10.7)	444 (9.1)	994 (11.6)	<0.01	
COPD /respiratory insufficiency (%)	2339 (17.4)	907 (18.6)	1432 (16.7)	<0.01	
Renal insufficiency (%)	1261 (9.4)	399 (8.2)	862 (10.1)	<0.01	
Liver cirrhosis (%)	178 (1.3)	61 (1.2)	117 (1.4)	0.62	
Malignancy including hematologic malignancies (%)	869 (6.5)	353 (7.2)	516 (6.0)	<0.01	
Immunodeficiency (%)	979 (7.3)	400 (8.2)	579 (6.8)	<0.01	
Admission characteristics					
APACHE IV estimated mortality rate (IQR)	0.7 (0.3–0.9)	0.7 (0.3–0.9)	0.7 (0.3–0.9)	<0.01	87 (0.65)
Admission type				0.02	54 (0.40)
Medical	10,113 (75.4)	3617 (74.3)	6496 (76.1)		
Urgent surgical	1957 (14.6)	725 (14.9)	1232 (14.4)		
Elective surgical	1337 (10.0)	528 (10.8)	809 (9.5)		
GCS *on admission*				0.87	2774 (21%)**
GCS ≤ 5 (%)	5479 (51.3)	2003 (51.4)	3479 (51.2)		
GCS 6–14 (%)	1794 (16.8)	645 (16.5)	1149 (16.9)		
GCS 15 (%)	3414 (31.9)	1251 (32.1)	2163 (31.9)		
Diagnosis on admission					0 (0.0)
Mechanical ventilation (%)	11,013 (81.8)	3928 (80.3)	7085 (82.7)	<0.01	
CVA (%)	464 (3.4)	178 (3.6)	286 (3.3)	0.38	
Intracranial mass (%)	269 (2.0)	114 (2.3)	155 (1.8)	0.04	
Gastro intestinal bleeding (%)	351 (2.6)	126 (2.6)	225 (2.6)	0.91	
Diabetes (%)	2563 (19.0)	972 (19.9)	1591 (18.6)	0.06	
GCS *at 24 h of ICU admission*				0.1	2839 (21%)**
GCS ≤ 5 (%)	4735 (44.6)	1687 (43.6)	3048 (45.2)		
GCS 6–14 (%)	1658 (15.6)	592 (15.3)	1066 (15.8)		
GCS 15 (%)	4229 (39.8)	1594 (41.2)	2635 (39.0)		
Diagnosis at 24 h of ICU admission					0 (0.0)
AKI (%)	2929 (21.8)	1028 (21.0)	1901 (22.2)	0.13	
Mechanical ventilation (%)	11,681 (86.8)	4184 (85.6)	7497 (87.5)	<0.01	
Infection (%)	2055 (15.3)	765 (15.6)	1290 (15.0)	0.37	
Vasoactive medication (%)	9762 (72.5)	3457 (70.7)	6305 (73.6)	<0.01	
Thrombolytic therapy (%)	591 (4.4)	203 (4.2)	388 (4.5)	0.33	
Academic hospital (%)	3305 (24.6)	1132 (23.2)	2173 (25.3)	<0.01	0 (0.0)

IHCA: in-hospital cardiac arrest, BMI: body-mass index, COPD: chronic obstructive pulmonary disease, APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Coma Scale, CVA: cerebrovascular accident, AKI: acute kidney injury.
** The Glasgow Coma Scale (GCS) at admission and 24 h after ICU admission were measured only in earlier years of the NICE registry. It was decided to stop collection of the GCS data in recent years. For this reason, the number of missing values is large. Nevertheless, we decided to present the data that is available, but not use it in our multivariable models.
^The missing values for women and men are presented separately in Supplementary Digital Content Table H (IHCA).

3.4. Cox proportional hazard regression results

Table 4 presents the Cox proportional hazard regression results for OHCA and IHCA. Next to our estimates for sex differences we found some notable results. As for OHCA, we found that increasing age is positively associated with 1-year mortality. Further, we found that liver cirrhosis (HR 2.01, 95% CI 1.70–2.38) and intracranial mass (HR 3.06, 95% CI 2.73–3.44) are both positively associated with 1-year mortality. As for IHCA, we also found that increasing age is positively associated with 1-year mortality.

3.5. The proportional hazard assumptions

Table 5 presents the HRs for the left-truncation analysis. As for OHCA, the adjusted HR estimated with left-truncation at hospital

Table 3
Clinical outcomes for OHCA and IHCA patients, for women and men.

	Total	Women	Men	p-value	Missing values (%)
OHCA					
Length of ICU stay in hours (IQR)	66.7 (25.2–127.7)	56.9 (19.4–118.4)	69.9 (29.5–132.9)	<0.01	0 (0.0)
Hospital length of stay in days (IQR)	5.5 (1.9–14.4)	4.2 (1.4–12.5)	6.2 (2.2–15.1)	<0.01	31 (0.2)
ICU mortality (%)	8814 (45.3)	3170 (53.0)	5644 (41.9)	<0.01	0 (0.0)
Hospital mortality (%)	9690 (49.8)	3432 (57.4)	6258 (46.5)	<0.01	0 (0.0)
1-year mortality (%)	10,909 (56.1)	3821 (63.9)	7088 (52.6)	<0.01	0 (0.0)
IHCA					
Length of ICU stay in hours (IQR)	50.5 (17.1–133.2)	45.9 (14.4–117.8)	54.9 (18.5–139.4)	<0.01	1 (0.01)
Hospital length of stay in days (IQR)	6.0 (1.5–15.1)	5.3 (1.3–14.1)	6.4 (1.7–15.6)	<0.01	27 (0.20)
ICU mortality (%)	5846 (43.4)	2256 (46.1)	3590 (41.9)	<0.01	0 (0.0)
Hospital mortality (%)	6670 (49.6)	2541 (52.0)	4129 (48.2)	<0.01	0 (0.0)
1-year mortality (%)	7823 (58.1)	2935 (60.0)	4888 (57.0)	<0.01	0 (0.0)

Table 4
Multivariable Cox regression analysis for 1-year mortality in OHCA and IHCA patients***.

		OHCA	IHCA
Women		1.28 (1.23–1.34)	1.09 (1.04–1.14)
Age	<40	Reference	Reference
	40–50	0.88 (0.79–0.98)	0.86 (0.74–1.01)
	50–55	0.89 (0.79–0.99)	1.04 (0.88–1.21)
	55–60	0.92 (0.83–1.03)	1.02 (0.88–1.19)
	60–65	1.04 (0.94–1.15)	1.16 (1.01–1.34)
	65–70	1.18 (1.07–1.30)	1.33 (1.16–1.53)
	70–80	1.44 (1.32–1.58)	1.57 (1.38–1.79)
	80–90	2.29 (2.08–2.52)	2.15 (1.88–2.46)
	>90	3.11 (2.64–3.66)	2.78 (2.25–3.45)
BMI	<20	1.11 (1.04–1.18)	1.12 (1.04–1.20)
	20–25	Reference	Reference
	25–27.5	1.00 (0.97–1.10)	1.01 (0.94–1.09)
	27.5–30	0.95 (0.89–1.01)	0.91 (0.84–0.98)
	>30	1.04 (0.97–1.10)	0.97 (0.90–1.04)
Medical history	Cardiovascular insufficiency	1.01 (0.94–1.09)	1.17 (1.09–1.25)
	COPD /respiratory insufficiency	1.36 (1.30–1.43)	1.22 (1.15–1.29)
	Renal insufficiency	1.34 (1.24–1.45)	1.24 (1.15–1.33)
	Liver cirrhosis	2.01 (1.70–2.38)	1.55 (1.30–1.84)
	Malignancy including hematologic malignancies	1.86 (1.68–2.06)	1.78 (1.64–1.94)
	Immunodeficiency	1.12 (1.02–1.23)	1.25 (1.15–1.35)
Diagnosis on admission	Mechanical ventilation	1.27 (1.17–1.37)	1.25 (1.17–1.34)
	CVA	1.32 (1.19–1.48)	1.19 (1.06–1.35)
	Intracranial mass	3.06 (2.73–3.44)	1.55 (1.33–1.80)
	Gastro intestinal bleeding	1.50 (1.30–1.72)	1.53 (1.34–1.73)
	Diabetes Mellitus	1.24 (1.89–1.30)	1.15 (1.09–1.22)
GCS on admission	<5	2.18 (2.01–2.36)	2.61 (2.45–2.79)
	6–14	0.83 (0.75–0.92)	1.37 (1.26–1.49)
	15	Reference	Reference
N		19,440	13,461
-2 Loglikelihood		203,812.30	140,306.83
Likelihood ratio test p-value		<0.01	<0.01
AIC		203,868.30	140,362.83

Note: estimates are Hazard Ratios (HR) and 95% Confidence Interval (95% CI), derived from a Cox proportional hazard regression analysis. OHCA: out of hospital cardiac arrest, IHCA: in-hospital cardiac arrest, BMI: body mass index, CVA: cerebrovascular accident, GCS: Glasgow Coma Scale. ***Number of patients per sub-group for the categories for age, BMI, and GCS are presented in Supplementary Digital Content Table I. The number of patients for medical history and diagnosis on admission are presented in Tables 1 and 2 in the main text.

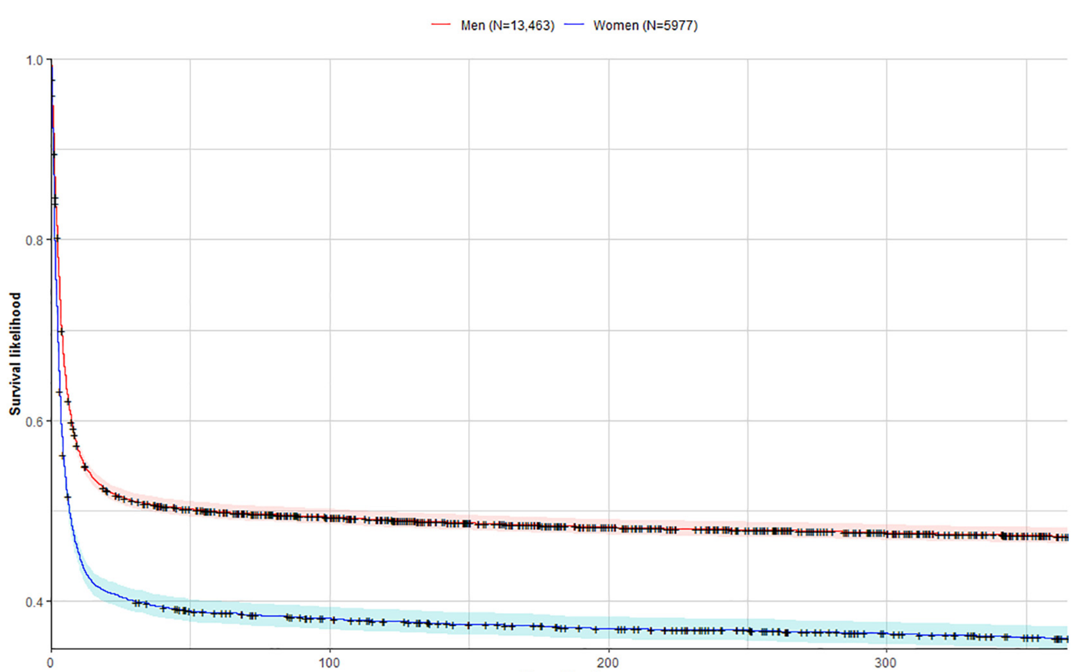

Fig. 1. 1-year mortality of women vs men in OHCA patients, Log-rank test $p < 0.01$.

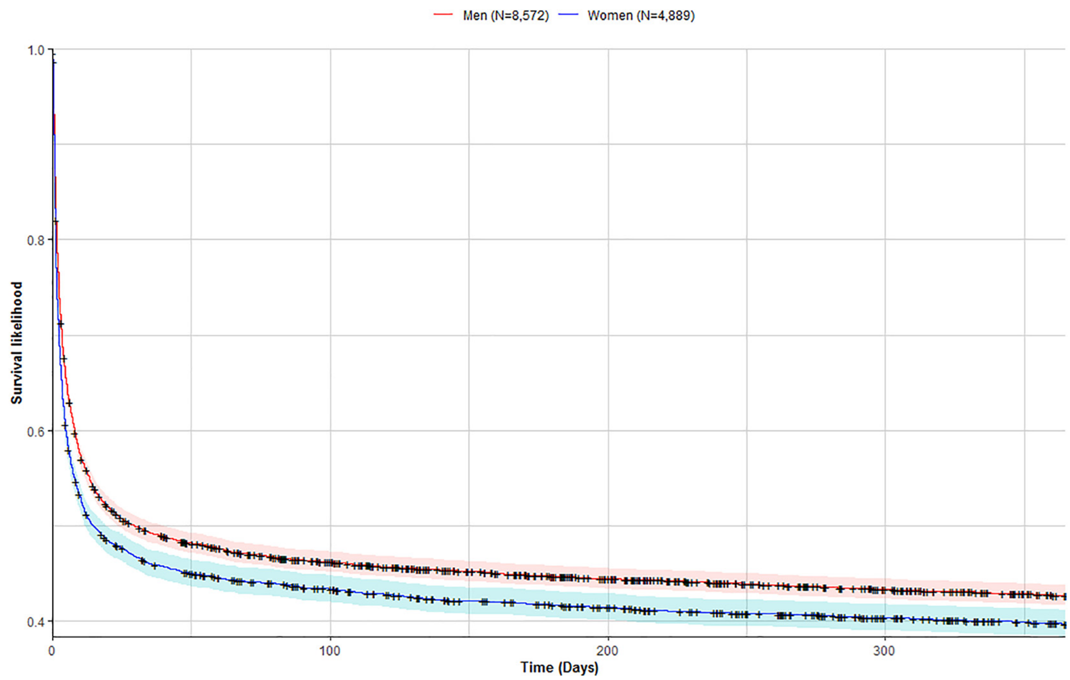

Fig. 2. 1-year mortality of women vs men in IHCA patients, Log-rank test $p < 0.01$.

discharge remains statistically significant and in the same magnitude as compared to no left-truncation (HR 1.37, 95% CI 1.25–1.49). Although the magnitude of the HRs are similar across the increasing left-truncation thresholds, the statistical significance over the truncation thresholds disappear. This is likely due to the decreasing sample size after left-truncation. For OHCA, we provide evidence that the proportional hazard assumption holds. Supplementary Digital Content Fig. E shows the survival curves for OHCA patients when the increasing left-truncation thresholds are applied.

As for IHCA, the adjusted HRs estimated with left-truncation at the different thresholds are statistically insignificant and smaller as compared to no left-truncation. For IHCA, we found some evidence that the proportional hazard assumption is violated. Supplementary Digital Content Fig. F shows the survival curves for OHCA patients when the increasing left-truncation thresholds are applied.

4. Discussion

This nationwide study showed that women who are admitted to the ICU after both OHCA and IHCA have a higher 1-year mortality than men. After left-truncation, for OHCA we found that the HRs remained relatively constant suggesting a persistent effect of sex on mortality during the first year after CA. At the same time for IHCA, after left-truncation, the effect of sex was mainly present in the initial phase after CA but decreases at later stages of follow-up. Our results suggests that the effect of sex on mortality during all intervals of the first year is more pronounced in OHCA than in IHCA patients.

Other studies comparing 1-year mortality in women and men in OHCA and IHCA are scarce and performed in smaller samples. Mc Laughlin et al. [32] investigated long-term mortality in hospital survivors of a combined sample of OHCA and IHCA patients ($n = 1433$). They found a significantly higher mortality rate in women (53%) than

Table 5
Cox proportional hazard regressions for 1-year mortality at different left-truncation thresholds.

OHCA			Women	Men
	Crude	Adjusted	N_{total} ($N_{non\text{-}survivors}$, % survival)	N_{total} ($N_{non\text{-}survivors}$, % Survival)
No left truncation	1.39 [1.34–1.45]	1.28 [1.23–1.33]	5977 (3821, 64%)	13,463 (7088, 53%)
Left truncation at:				
At hospital discharge	1.51 [1.39–1.64]	1.37 [1.25–1.49]	3021 (879, 29%)	7975 (1636, 21%)
At 30 days	1.37 [1.17–1.59]	1.21 [1.04–1.42]	2390 (238, 10%)	6859 (506, 7%)
At 90 days	1.33 [1.08–1.63]	1.19 [0.96–1.47]	2257 (132, 6%)	6560 (290, 4%)
At 180 days	1.41 [1.06–1.87]	1.31 [0.98–1.76]	2160 (70, 3%)	6293 (146, 2%)
At 270 days	1.45 [0.98–2.16]	1.39 [0.93–2.08]	2079 (37, 2%)	6124 (75, 1%)
IHCA				
	Crude	Adjusted	Women	Men
No left truncation	1.11 [1.06–1.16]	1.09 [1.04–1.14]	4889 (2935, 60%)	8572 (4888, 57%)
Left truncation at:				
At hospital discharge	0.99 [0.90–1.09]	0.97 [0.88–1.07]	2606 (668, 26%)	4904 (1256, 26%)
At 30 days	1.04 [0.91–1.19]	1.01 [0.88–1.15]	2277 (334, 15%)	4260 (598, 14%)
At 90 days	1.10 [0.92–1.33]	1.05 [0.87–1.27]	2086 (177, 8%)	3904 (300, 8%)
At 180 days	1.07 [0.82–1.38]	1.03 [0.79–1.36]	1952 (90, 5%)	3659 (158, 4%)
At 270 days	1.06 [0.72–1.55]	1.04 [0.70–1.55]	1847 (41, 2%)	3465 (73, 2%)

in men (43%, $p < 0.01$), at a median follow up of 3.6 years. [32] This effect disappeared after adjustment for baseline covariates including cardiac characteristics (HR 1.05, 95% CI 0.85–1.29). Wissenberg et al. [33] showed a significantly higher unadjusted mortality rate ($p < 0.01$) in EMS-treated OHCA in women than in men. These mortality rates are much higher than the mortality rates we found, which is probably due to the difference in included patients (EMS-treated versus ICU-admitted CA patients). Another study performed by Lindgren et al. [23] among 1498 OHCA patients showed no difference in 1-year mortality rate between women and men. We could not find studies comparing 1-year mortality in women and men only including IHCA patients. Schluep et al. [28] performed a meta-analysis and found an overall 1-year mortality of 82.4%, but these studies also included patients who died before ICU admission. A meta-analysis of Fennessy et al. [34] showed a very low overall 1-year mortality of 3.0–14.3%, however they only included hospital survivors. In another study performed by Schluep et al. [26] performed in a single centre a 1-year mortality of 74% was found in ICU admitted IHCA patients.

Our secondary outcome was hospital mortality, which we also found to be higher in women than in men in both OHCA and IHCA. Sex differences in hospital mortality have been described more often. John et al. [22] combined OHCA and IHCA patients and found equal hospital mortality rates in women (21%) and in men (23%, $p = 0.68$). Unfortunately, they did not stratify for OHCA/IHCA, their sample size was smaller, and was focussed on patients undergoing a coronary angiogram. Many recent studies in OHCA patients found a higher mortality in women in univariable analyses but not in multivariable analyses. [12,14,17,19,21,24,35] However, some studies did find a multivariable adjusted significantly higher mortality for women while correcting for cardiac characteristics, e.g., primary cardiac rhythm. [18,36,37] This disparity could be explained by cardiac factors in the causal pathway, which we could not adjust for. In our study hospital mortality rates in women after IHCA were higher than in men. Just few studies have been examining sex differences in IHCA patients. For example, Al Dury et al. [13] found higher mortality rates for women in their univariable analysis, but not in the multivariable analysis (OR 0.96, 95% CI 0.85–1.09). In a smaller study performed by Qvick et al. [38], no differences were shown in the univariable as well as the multivariable analysis. This could be due to the low proportions of women and men with shockable primary rhythm (18% vs. 21%, respectively).

It is not straightforward to explain the findings regarding sex differences in mortality after OHCA and IHCA of our study and recent literature. The differences in findings could be due to many factors, such as: heterogeneity of the aimed population, inclusion and exclusion criteria, sample sizes, studied cardiac characteristics, awareness of bystanders, and prehospital, and in-hospital treatment differences between countries and hospitals. In most studies, primary cardiac rhythm seems to be an important contributing factor of the differences in mortality between women and men. Shockable primary cardiac rhythms are less often present in women than in men in both OHCA and IHCA. [12-21,24,33,37,38] A shockable primary cardiac rhythm is more often present in OHCA patients than in IHCA patients, and OHCA patients have higher probability of CA due to a cardiac aetiology than IHCA patients. [39-41] However, Sheak et al. [40] also found a higher probability of asystole as primary cardiac rhythm in OHCA patients than in IHCA patients. These authors did not present delay before start of CPR and occurrence of bystander CPR, which could have caused the shockable primary cardiac rhythms to be already converted to asystole. Finally, it may also be the case that there is some bias with respect to the treatment and care of women after cardiac arrest. Although, we attempted to include as much information about treatment, this should be confirmed in future studies.

Since the primary cardiac rhythm was not available in our study, we were not able to adjust for this factor. Therefore, we can only speculate if this is the only factor responsible for the sex differences that we found in both OHCA and IHCA. The general occurrence of a shockable primary cardiac rhythm and cardiac cause in IHCA is lower. Hence, the sex difference we found is most probably not only due to the primary cardiac rhythm. However, our results were indeed less pronounced in IHCA. With our results in mind, we hypothesise that despite the expected difference in primary cardiac rhythm and cause of arrest, the pathophysiology in women may also be different. The question investigating the cause of the sex difference would therefore be an important aim for future research. More detailed knowledge could result in a different approach and more specified treatment for women and men.

4.1. Limitations

We have previously discussed the limitations of the use of the NICE registry for studying CA. [25] For this study the most important limitation is the absence of cardiac characteristics, especially the unknown primary cardiac rhythm, the cause of CA, and time to ROSC. These factors may, at least in part, explain the observed differences. Other limitations include that, in the NICE registry, the location of arrest (OHCA or IHCA) is not registered. Therefore, we had to determine this with the best possible approximation using the admission origin. Next, we could only report mortality rates in this study, because there were no data available on neurological outcomes or quality of life after hospital discharge. Further, the statistically significant shorter length of stay we found in women is most probably due to the higher mortality in these patients. Finally, the increasing age of both OHCA and IHCA could influence the 1-year mortality. This mortality could be caused by other age-related problems and not be a result of the CA. The mortality rates will probably be for some part overestimate the mortality caused by OHCA or IHCA.

5. Conclusion

Women admitted to the ICU after cardiac arrest have a higher mortality rate than men. After left-truncation, we found that this sex difference persisted for OHCA. For IHCA we found that the effect of sex was mainly present in the initial phase after the cardiac arrest.

Declaration of Competing Interest

FT and NdK work at the department of medical informatics of Amsterdam University Medical Center. This department is paid by the Netherlands Intensive Care Evaluation (NICE) registry to process the data of the individual Intensive Care Units (ICUs) into the national database and to perform analyses and produce benchmark information. The remaining authors have disclosed that they do not have any conflicts of interest. Other authors have no conflict of interest to declare.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.04.007.

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