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Clinical paper

Effect of cancer history on post-resuscitation treatments in out-of-hospital cardiac arrest

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Abstract

Objectives: There is growing evidence that optimal post-resuscitation treatment is a significant factor for overall survival and neurological outcomes in out-of-hospital cardiac arrest (OHCA). However, there is also growing evidence of disparities in treatments in vulnerable populations such as elderly individuals or patients with underlying diseases, including cancer.

Aim: The aim of this study was to evaluate the influence of cancer status on post-resuscitation therapies among OHCA patients.

Material and methods: This was a cross-sectional observational study based on a nationwide prospective OHCA registry database of Korea. All adult OHCA patients with presumed cardiac etiology and sustained return of spontaneous circulation (ROSC) from 2009 to 2016 were included in this study. Main exposure was history of cancer and primary outcome was post-resuscitation care, including percutaneous coronary intervention (PCI) and targeted temperature management (TTM). Multivariable logistic regression was used to analyze the association between cancer and post-resuscitation treatments.

Results: A total of 33,760 patients were included for final analysis. Multivariable logistic analysis showed that cancer patients were significantly less likely to receive PCI and TTM compared to those without history of cancer with adjusted odds ratios of 0.29 (95% CI: 0.24–0.37) and 0.66 (0.58–0.77), respectively.

Conclusion: The results of this study suggest that a prior history of cancer may be associated with lower probability to receive potentially beneficial post-resuscitation treatments.

Keywords: Cancer, Out-of-hospital cardiac arrest, Percutaneous coronary intervention, Targeted temperature management, Post-resuscitation treatments

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Introduction

Out-of-hospital cardiac arrest (OHCA) is a major public health problem with high socioeconomic cost.[1,2] With the growth of the aging population globally, the incidence of OHCA is expected to be increased further. Although survival rates of OHCA are highly variable, previous studies have reported increased rates of return of spontaneous circulation (ROSC) and survival following OHCA through advances in emergency medical services (EMS) systems and resuscitation technology over the past several decades.[3,4] However, a substantial proportion of OHCA deaths occur during post-resuscitation phase, among those patients who have been successfully resuscitated.[5] There is growing evidence that optimal post-resuscitation treatment strategies, including immediate coronary angiography (CAG) with percutaneous coronary intervention (PCI) and targeted temperature management (TTM), improve the survival outcomes in OHCA.[6,7]

Due to the aging and growth of the population, the number of patients with cancer and global burden of cancer are also rapidly growing.[8] The International Agency for Research on Cancer recently reported that the global cancer burden is estimated to be risen to 18.1 million new cases and 9.6 million new cancer deaths worldwide in 2018.[9] They further reported that one in 5 men and one in 6 women develop cancer during their lifetime, and one in 8 men and one in 11 women die from cancer. As well as increases in cancer incidence, the number of cancer survivors continues to grow because of advances in early detection and treatments.[10] Consequently, as the frequency of OHCA increases with age and the proportion of cancer survivors also increases, the number of patients with history of cancer who experience OHCA is also likely to increase.[11]

There is growing evidence of disparities in treatments in vulnerable populations such as elderly individuals or patients with underlying diseases, including cancer.[12–14] A recent study observed differences in acute treatments of acute myocardial infarction (AMI) patients, including immediate drug therapies and revascularization intervention, between cancer survivors and patients without a history of cancer.[13] In the study, the cancer patients were less likely to receive guideline recommended treatments and had higher in-hospital mortality than non-cancer patients. However, there have been limited studies which explored the influence of pre-arrest cancer status on post-resuscitation treatments received following OHCA. The objective of this study was to evaluate the influence of cancer status on post-resuscitation therapies among OHCA patients. We hypothesized that OHCA patients with cancer would receive less post-resuscitation treatments than those without cancer.

Methods

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1103-153-357). The Korea Centers for Disease Control and Prevention (CDC) approved the use of the national OHCA registry data in this study.

Study design and data source

This was a cross-sectional observational study based on a nationwide prospective OHCA registry database of Korea. The registry was developed by the Korea Centers for Disease Control and Prevention (CDC) in 2006. The registry contains data for all EMS-treated OHCA patients in Korea from the EMS run sheets and in-depth cardiac arrest EMS registry, which provide ambulance operation information and Utstein factors. Hospital care, including post-resuscitation, and survival outcomes are collected by retrospective medical record review by trained medical record reviewers. EMS run sheets, EMS cardiac arrest registries and national OHCA registry are all included in the nationwide OHCA registry database and stored in each provincial EMS headquarters as electronic forms.[15,16] The quality management is conducted by the Korea CDC Data Quality Control (DQC) team composed of emergency medicine physicians, EMS physicians, epidemiologists, statistical experts, and professional medical record reviewers. The quality management team educated all medical record reviewers before starting the project, provided the reviewers a standard manual for data extraction, monthly feedback to ensure the data quality and consultation on ambiguous cases.[17]

Study setting

The Korean EMS system is the national fire department-operated and has 16 provincial headquarters. Approximately 1350 ambulance stations cover 100,000 square kilometers and 51 million people, and the mean time interval from call to arrival and from arrival to transport both are about 6 min.[18] All ambulances offer single-tiered Basic Life Support (BLS) to OHCA patients at the scenes following the EMS CPR protocol staffed by emergency medical technicians (EMTs). All OHCA patients are recommended to transport to the nearest hospital emergency department (ED) because only doctors can declare death under the Korean system.

The ED levels are designated by the government from level 1 to 3 based on ED characteristics including human resources, essential equipment, level of service, and size of department. Most level 3 EDs are operated by general physicians and provide basic emergency care. According to the law, emergency physicians are prepared for 24 h a day and provide advanced emergency care services in level 1 or 2 EDs. Especially level 1 EDs are always available for emergency treatment of acute myocardial infarction and stroke. There are 21 level 1 EDs, and approximately 120 level 2 EDs and 340 level 3 EDs in Korea and they all are re-evaluated annually.[19]

Study population

This study included all EMS-assessed patients with OHCA of suspected cardiac etiology who were 18 years of age or older from 2009 to 2016. Patients with age younger than 18 years, non-cardiac etiology, no sustained ROSC, and unknown information on PCI and/or TTM were excluded.

Main outcomes

The primary outcome was post-resuscitation care, including PCI and TTM. The secondary outcomes were survival at discharge and good neurological recovery. Good neurological recovery was defined as cerebral performance category (CPC) score of 1 (Good Cerebral Performance: Conscious, alert, able to work and lead a normal life. May have minor psychologic or neurologic deficits) or 2 (Moderate Cerebral Disability: Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life. May have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes) at discharge.[20] Both

outcomes were reviewed by medical record reviewers based on hospital records described by physician.

Measurements

The main exposure of interest was history of cancer. Cancer status (whether the patient has a prior history of cancer or not) is recorded in the hospital medical records. To evaluate medical records, trained professional medical record reviewers from the Korean CDC visited all of the hospitals and collect the records electronically.

We also collected other variables: gender, age, residential area, season (spring, summer, autumn, and winter), day of the week (weekends or weekdays), time of the day (0600–1759 as day or 1800-0559 as night), past medical history (diabetes mellitus, hypertension, heart disease and stroke), place of arrest (public, private, and ambulance), witnessed status, bystander CPR, primary ECG rhythm at the scene (shockable rhythm or not), bystander defibrillation, EMS defibrillation, EMS response time interval (time interval from call to arrival of ambulance at the scene), scene time interval (time interval from arrival at and departure from the scene), transport time interval (time interval from departure from the scene to arrival at the ED), time interval from EMS call to ROSC, levels of ED (levels 1 or 2 and 3), post-resuscitation treatment and survival outcomes.

Statistical analysis

The distributions of selected characteristics were compared by cancer status. Categorical variables were reported as number and percentage (%) and analyzed with Chi-square test. Continuous variables were reported as median and interquartile rage (IQR) and analyzed with Wilcoxon rank sum test. To analyze the significance of the yearly trend of use of PCI and TTM, Poisson test for trend was used. Multivariable logistic regression was used to determine the association between cancer status and post-resuscitation treatments, PCI and TTM, which estimated adjusted odds ratios (AORs) and 95% confidence intervals (CIs). We considered all possible confounding factors, including demographic (age, gender, comorbidities), time factors (year of arrest, season, day of the week and time of arrest), community factors (residential area), Utstein, EMS factors and hospital factors.

We also performed subgroup analyses for the evaluation of interaction effects of cancer with PCI and TTM on outcomes. A two-tailed p value <0.05 was considered to be statistically significant. All data were analyzed by using SAS 9.4 (SAS institute Inc., NC, USA).

Results

Demographic characteristics

Among 204,090 EMS-assessed OHCAs in South Korea during the study period, 33,760 patients were included for the final analysis, after excluding patients younger than 18 years of age (n = 4757), non-cardiac etiology (n = 54,609), no sustained ROSC (n = 110,964) and unknown treatment status (n = 0) (Fig. 1).

Of these 33,760 patients, OHCAs with history of cancer was 3453 (10.2%) and 30,307 (89.8%) were non-cancer patients. More patients were male in both cancer (68.2%) and non-cancer (65.8%) groups and cancer patients had a higher median age than non-cancer patients (70.4 (IQR 60.1–77.3) vs. 65.9 (53.5–76.7), $p < 0.01$). The season, week (weekday vs. weekend), day (daytime vs. nighttime), and metropolitan city of arrest occurred were statistically nonsignificant by cancer status. Non-cancer patients had more past medical history than cancer patients with hypertension (39.7% vs. 33.9%, $p < 0.01$), heart disease (18.4% vs. 12.0%, $p < 0.01$), and stroke (9.3% vs. 6.4%, $p < 0.01$).

Non-cancer patients had higher rates of primary shockable rhythm (22.1% vs. 10.6%, $p < 0.01$), received more percutaneous coronary intervention (PCI) (8.7% vs. 2.5%, $p < 0.01$) and targeted temperature management (TTM) than cancer patients (10.3% vs. 6.5%, $p < 0.01$) (Table 1).

Fig. 2 shows yearly trends in utilization of PCI and TTM between 2011 and 2016 in cancer and non-cancer patients. From 2011 to 2016, the use of PCI significantly increased from 7.7% to 10.2% ($p_{trend}<0.01$) in non-cancer patients, while there was non-significant changes ($p_{trend} = 0.06$) in utilization of PCI in cancer patients. For TTM,

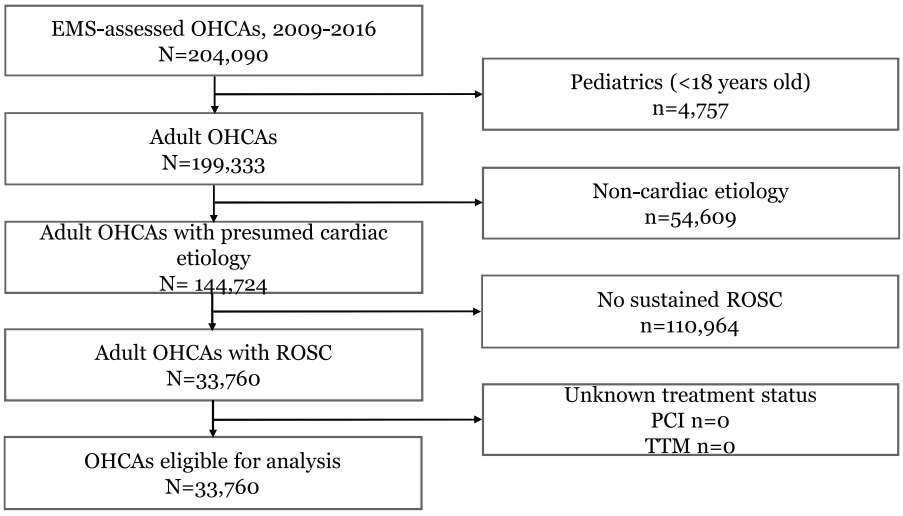

Fig. 1 – Study population.
Abbreviations: EMS = emergency medical services; OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; PCI = percutaneous coronary intervention; TTM = targeted temperature management.

Table 1 – Baseline characteristics by cancer status.

	Total		Cancer status				P-value*
			Cancer		Non-cancer		
	N	%	N	%	N	%	
Total	33,760	(100.0)	3453	(10.2)	30,307	(89.8)	
Male	22,292	(66.0)	2354	(68.2)	19,938	(65.8)	0.01
Age, year, median (IQR)	66.6 (54.1–76.8)		70.4 (60.1–77.3)		65.9 (53.5–76.7)		<0.01
18–64	15,835	(46.9)	1220	(35.3)	14,615	(48.2)	<0.01
65–74	7897	(23.4)	1111	(32.2)	6786	(22.4)	
75 and older	10,028	(29.7)	1122	(32.5)	8906	(29.4)	
Metropolitan	18,103	(53.6)	1865	(54.0)	16,238	(53.6)	0.63
Season							0.46
Spring	8545	(25.3)	905	(26.2)	7640	(25.2)	
Summer	7790	(23.1)	798	(23.1)	6992	(23.1)	
Autumn	8359	(24.8)	856	(24.8)	7503	(24.8)	
Winter	9066	(26.9)	894	(25.9)	8172	(27.0)	
Week							0.35
Weekdays	23,908	(70.8)	2469	(71.5)	21,439	(70.7)	
Weekends	9852	(29.2)	984	(28.5)	8868	(29.3)	
Day							0.44
Day	13,501	(40.0)	1402	(40.6)	12,099	(39.9)	
Night	20,259	(60.0)	2051	(59.4)	18,208	(60.1)	
Past medical history							
Diabetes Mellitus	8741	(25.9)	866	(25.1)	7875	(26.0)	0.25
Hypertension	13,212	(39.1)	1172	(33.9)	12,040	(39.7)	<0.01
Heart	6000	(17.8)	413	(12.0)	5587	(18.4)	<0.01
Stroke	3030	(9.0)	221	(6.4)	2809	(9.3)	<0.01
Place of arrest							<0.01
Public	5698	(16.9)	279	(8.1)	5419	(17.9)	
Private	25,143	(74.5)	2794	(80.9)	22,349	(73.7)	
Ambulance	2919	(8.6)	380	(11.0)	2539	(8.4)	
Witnessed	6242	(18.5)	612	(17.7)	5630	(18.6)	0.25
Bystander CPR	11,504	(34.1)	1111	(32.2)	10,393	(34.3)	0.01
Primary shockable rhythm at the scene	7076	(21.0)	367	(10.6)	6709	(22.1)	<0.01
Bystander defibrillation	223	(0.7)	15	(0.4)	208	(0.7)	0.08
EMS defibrillation	8439	(25.0)	510	(14.8)	7929	(26.2)	<0.01
EMS time, min, median (IQR)							
Response time interval	6.0 (5.0–8.0)		6.0 (5.0–8.0)		6.0 (5.0–8.0)		0.33
Scene time interval	7.0 (5.0–11.0)		8.0 (5.0–11.0)		7.0 (5.0–11.0)		<0.01
Transport time interval	6.0 (4.0–10.0)		6.0 (4.0–10.0)		6.0 (4.0–10.0)		0.02
Time from EMS call to ROSC, median (IQR)	17.0 (12.0–23.0)		18.0 (12.0–26.0)		16.0 (12.0–22.0)		<0.01
Level of ED							0.86
Level 1 or 2	27,540	(81.6)	2813	(81.5)	24,727	(81.6)	
Post-resuscitation treatment							
PCI	2714	(8.0)	86	(2.5)	2628	(8.7)	<0.01
TTM	3331	(9.9)	224	(6.5)	3107	(10.3)	<0.01
Outcomes							
Survival to discharge	7843	(23.2)	409	(11.8)	7434	(24.5)	<0.01
Good neurological recovery	4120	(12.2)	163	(4.7)	3957	(13.1)	<0.01

there was a trend of increasing utilization of TTM from 2009 to 2012 and then decreased utilization from 2011 to 2016 for both cancer and non-cancer groups with non- significant increase or decrease ($p_{trend} = 0.83$ for cancer group and $p_{trend} = 0.17$ for non-cancer group).

Associations between history of cancer status and study outcomes

Multivariable logistic regression analysis showed that cancer patients were significantly less likely to receive PCI and TTM compared to those without history of cancer with AORs (95% CIs) of 0.29 (0.24–0.37) for PCI and 0.66 (0.58–0.77) for TTM (Table 2).

For survival outcomes, compared with non-cancer patients, cancer patients were statistically significantly associated with lower survival to discharge and good neurological recovery with AORs (95% CIs) of 0.47 (0.42–0.53) and 0.39 (0.33–0.46), respectively (Table 2).

Interaction analysis

Table 3 shows the interaction effect between cancer status and PCI for the outcomes of survival to discharge and good neurological recovery.

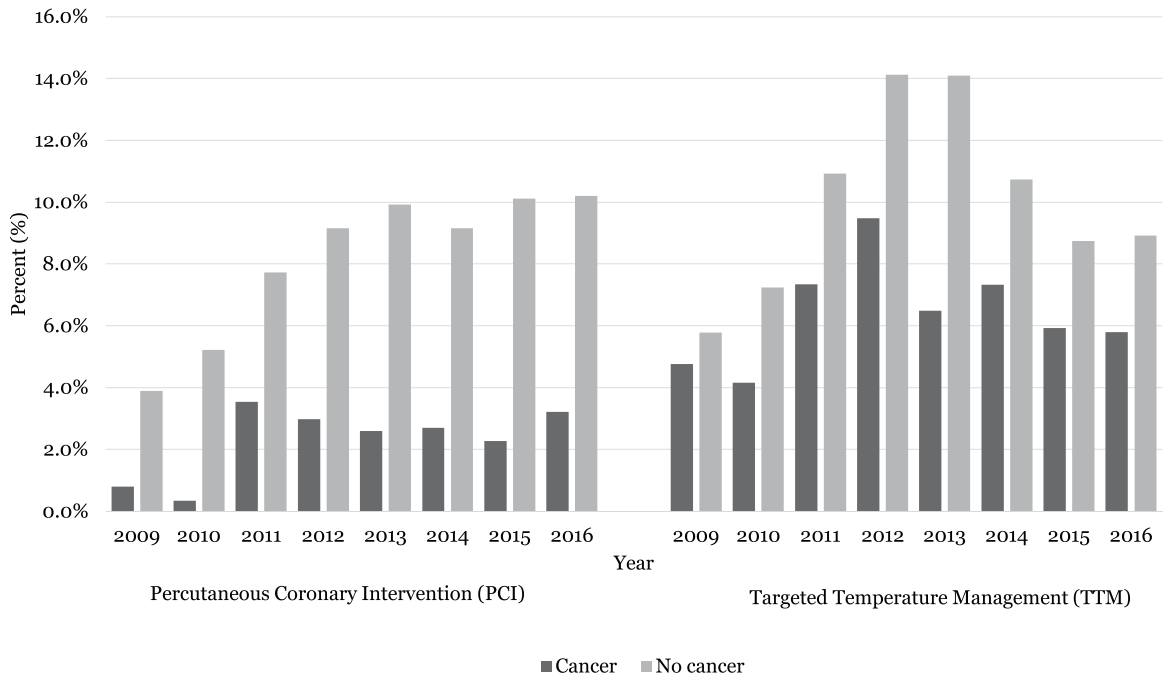

Fig. 2 – Trends in utilization of percutaneous coronary intervention (PCI) and targeted temperature management in out-of-hospital cardiac arrest (OHCA) patients from 2009 to 2016 by history of cancer status.

Table 2 – Associations between history of cancer status and study outcomes.

	n/N (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Any post-resuscitation care received			
Non-cancer	5258/30307 (17.3)	1.00	1.00
Cancer	294/3453 (8.5)	0.44 (0.39–0.50)	0.48 (0.43–0.55)
PCI			
Non-cancer	2628/30307 (8.7)	1.00	1.00
Cancer	86/3453 (2.5)	0.27 (0.22–0.33)	0.29 (0.24–0.37)
TTM			
Non-cancer	3107/30307 (10.3)	1.00	1.00
Cancer	224/3453 (6.5)	0.61 (0.53–0.70)	0.66 (0.58–0.77)
Survival to discharge			
Non-cancer	7434/30307 (24.5)	1.00	1.00
Cancer	409/3453 (11.8)	0.41 (0.37–0.46)	0.47 (0.42–0.53)
Good neurological recovery			
Non-cancer	3957/30307 (13.1)	1.00	1.00
Cancer	163/3453 (4.7)	0.33 (0.28–0.39)	0.39 (0.33–0.46)

[a] Adjusted for age, gender, year of arrest, season, week, time of arrest, metropolitan and comorbidities.

The AORs (95% CIs) for survival to discharge of cancer group without and with PCI were 0.76 (0.68–0.86) and 0.80 (0.64–1.01), respectively compared with the non-cancer group as the reference. The AORs (95% CIs) for good neurological outcome for cancer group without and with PCI were 0.75 (0.66–0.86) and 0.85 (0.67–1.08), respectively (Table 3).

The AORs (95% CIs) for survival to discharge for cancer group without and with TTM were 0.74 (0.69–0.80) and 0.81 (0.70–0.94), respectively with non-cancer group as the reference. The AORs (95% CIs) for good neurological outcome of cancer group without and with TTM were 0.68 (0.61–0.76) and 0.75 (0.61–0.91), respectively (Table 4).

Table 3 – Effects PCI on the association between cancer status and outcomes (survival and neurological recovery outcomes).

		Total N (%)	Positive outcome n/N (%)	Adjusted[a] OR (95% CI)
Survival to discharge				
PCI (–)		31046		
	Non-cancer	27679 (89.2)	5700/27679 (20.6)	1.00
	Cancer	3367 (10.8)	365/3367 (10.8)	0.76 (0.68–0.86)
PCI (+)		2714		
	Non-cancer	2628 (96.8)	1734/2628 (66.0)	1.00
	Cancer	86 (3.2)	44/86 (51.2)	0.80 (0.64–1.01)
Good neurological recovery				
PCI (–)		31046		
	Non-cancer	27679 (89.2)	2655/27679 (9.6)	1.00
	Cancer	3367 (10.8)	132/3367 (3.9)	0.75 (0.66–0.86)
PCI (+)		2714		
	Non-cancer	2628 (97.8)	1302/2628 (49.5)	1.00
	Cancer	86 (3.2)	31/86 (36.1)	0.85 (0.67–1.08)

Abbreviations: OR = odds ratio; CI = confidence interval; PCI = percutaneous coronary intervention.
[a] Adjusted for age, gender, year of arrest, season, week, time of arrest, metropolitan and comorbidities.

Table 4 – Effects TTM on the association between cancer status and outcomes (survival and neurological recovery outcomes).

		Total N	Positive outcome n/N(%)	Adjusted[a] OR (95% CI)
Survival to discharge				
TTM (–)		30429		
	Non-cancer	27200 (89.4)	5792 (21.3)	1.00
	Cancer	3229 (10.6)	323 (10.0)	0.74 (0.69-.0.80)
TTM (+)		3331		
	Non-cancer	3107 (93.3)	1642/3107 (52.9)	1.00
	Cancer	224 (6.7)	86/224 (38.4)	0.81 (0.70-0.94)
Good neurological recovery				
TTM (–)		30429		
	Non-cancer	27200 (89.4)	3099/27200 (11.4)	1.00
	Cancer	3229 (10.6)	130/3229 (4.0)	0.68 (0.61–0.76)
TTM (+)		3331		
	Non-cancer	3107 (93.3)	858/3107 (27.6)	1.00
	Cancer	224 (6.7)	33/224 (14.7)	0.75 (0.61–0.91)

Abbreviations: OR = odds ratio; CI = confidence interval; TTM = targeted temperature management.
[a] Adjusted for age, gender, year of arrest, season, week, time of arrest, metropolitan and comorbidities.

Discussion

This study shows that OHCA patients with history of cancer were less likely to undergo post-resuscitation treatments of PCI and/or TTM than the non-cancer counterparts.

Both PCI and TTM are widely used in the post-resuscitation cares of patients with cardiac arrests as prior studies have supported the beneficial effects of PCI [21,22] and TTM [23,24] in outcomes of OHCA patients. There is strong consensus on use of immediate coronary angiography with subsequent PCI in resuscitated patients of presumed cardiac cause.[25] The 2015 American Health Association (AHA) Guidelines Update strongly recommends that comatose OHCA patients with ROSC have TTM for both patients with shockable and non-shockable rhythms.[26] However, we observed OHCA patients with ROSC and a history of cancer were 71% and 37% less likely to receive PCI and TTM, respectively, compared with non-cancer OHCA patients with ROSC. Previously, a similar result was shown in a large cohort of adults in the Cardiac Arrest Registry of Enhance Survival (CARES). In the study, patients with cancer were 35% less likely to receive therapeutic hypothermia treatment after OHCA (4.66% vs. 7.14%; p = 0.001).[27]

One of main differences we observed between cancer and non-cancer groups was proportion of initial shockable rhythm. While about 10.6% of the OHCA patients with cancer had shockable rhythm at the scene, the proportion of non-cancer OHCA patients with shockable rhythm was 22.1%, which was more than twice that of the cancer group. There are several studies demonstrating an initial shockable rhythm as the independent indicator for PCI requirement because of benefits of this invasive approach in patients with shockable rhythm.[22,28] Disparities in the use of PCI and TTM observed in our study may be related to lower number of cancer patients with shockable rhythm. However, increasing studies support utilization of coronary intervention in cardiac arrest patients with non-shockable initial rhythms. [29] Similarly, benefits of therapeutic hypothermia in OHCA patients with initial non-shockable rhythms were also found in several studies.[30,31]

While little has been known regarding patterns of post-resuscitation care in OHCA patients with history of cancer, several previous studies have shown disparities in acute managements of AMI in those with a history of cancer. Rohrmann et al.[13] investigated whether AMI patients with a history of cancer received the same guideline recommended treatments as those AMI patients without cancer using a large prospective registry of patients with AMI in Switzerland (AMIS Plus). In the study, Rohrmann et al. found that AMI patients with a history of cancer were significantly less likely to undergo immediate therapy, including PCI (OR 0.76; 95% CI 0.67–0.88), or receive P2Y12 blockers (OR 0.82; 95% 0.71–0.94) and statins (OR 0.87; 95% CI 0.76–0.99) compared with those without history of cancer. They also found that this was associated with 45% higher in-hospital mortality rate among patients with a history of cancer compared with those without cancer with cardiac death as the main cause for both groups. Previously, similar effects of coronary intervention on achieving early reperfusion were observed in both cancer and non-cancer patients.[32] Another study also confirmed the benefit of guideline-recommended therapies for cancer patients with an acute ST-segment elevation myocardial infarction (STEMI) in terms of cardiovascular outcomes, suggesting an importance of aggressive cardiovascular care with them.[33]

In the present study, we found significantly lower survival to discharge and good neurological recovery outcomes among OHCA patients with a history of cancer compared with those without a cancer history. However, our interaction analysis showed that among those who received PCI, there was no significant differences in both survival to discharge and good neurological recovery outcomes between cancer and non-cancer OHCA patients. There are several previous studies supporting that cancer is not associated with mortality from OHCA. In a recent study,[11] Winther-Jensen et al. compared 30-day and 1-year mortality after successful resuscitation between patients with cancer prior to OHCA compared with those without a cancer history in a cohort of 993 Danish OHCA patients. In the study, cancer diagnosis was associated with higher crude mortality after OHCA. However, after adjustment for prognostic factors, including sex, age, primary rhythm, bystander witness, Charlson comorbidity index, and time to return of spontaneous circulation, cancer status was no more associated with higher mortality (hazard ratio (HR) 0.98, 95% CI 0.76–1.27 for 30-day mortality; HR 0.99, 95% CI 0.78–1.27 for 1-year mortality). Another study conducted in France[34] also found that the 6-month survival rate in patients with malignancies was not significantly different from that in a matched control group of patients with OHCA and without malignancies.

We had some limitations in this study. First, we did not have information on cancer, including type and stage of cancer, whether it is solid or hematologic cancer, and current treatment status. Therefore without detailed information on our cancer patients, we cannot rule out possibility of withholding comprehensive or invasive post-resuscitation therapies for patients with late stage or severe cancer.

Second, there were differences in the protocols for PCI procedure among the participating hospitals included in this study. While most EDs in Korea generally follow the international guidelines, there is no national standard protocol for reperfusion therapy. However, there is national standard protocol for TTM in Korea.[35]

Conclusion

The results of this study suggest that a prior history of cancer may be associated with lower probability to receive potentially beneficial post-ROSC treatments.

Conflict of interest statement

None.

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