Original article

Title

Potential Corneal Donation in Patients with Out-of-Hospital Cardiac Arrest: a Case-Control Study

Author name

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A short running title

POTENTIAL CORNEAL DONATION

Abstract

Aim: The shortage of corneal donations has been a longstanding problem in Japan. However, there are limited data on the settings in which corneal donations occur. The aim of this study was to determine the association between out-of-hospital cardiac arrest (OHCA) and corneal donation. We also investigated potential corneal donors across various death settings (OHCA, in-hospital cardiac arrest (IHCA) and home death).

Methods: We conducted a case-control study in Hiroshima Prefecture, Japan from 2015 to 2023. Cases included all corneal donors based on data provided by Hiroshima Eye Bank, while controls consisted of potential corneal donors in Hiroshima City Hiroshima Citizens Hospital. After matching cases with controls at a 1:5 ratio using age group, sex, and date of death, we employed unconditional logistic regression to analyze the association between OHCA and corneal donation.

Results: Among 4877 subjects, 190 were corneal donors and 3394 were potential corneal donors. Among corneal donors, 5.3% had OHCA, 26% had IHCA, and 29% died at home or in nursing homes. Of all subjects, 72% were potential corneal donors, with OHCA patients showing the highest proportion (75%). After adjusting matching factors, OHCA was positively associated with corneal donation (13% vs 15%; odds ratio: 2.2, 95% confidence interval: 1.3-3.5).

Conclusion: Individuals who experienced OHCA may be more likely than individuals in other settings of death to become corneal donors. Further research is needed to confirm the findings in this study and explore strategies to address the issue of Japan's corneal donation shortage.

Keywords

Case-control study; Corneal donation; Emergency department; Out-of-hospital cardiac arrest; Potential donor

Introduction

Corneal transplantation in Japan began officially in 1958 with government approval, and eye banks have been established in each prefecture of Japan.[1] As a result, corneal transplants are performed nationwide. However, the number of corneal donations in Japan has not increased over the past decade, and the number of patients waiting for corneal transplants has significantly exceeded the number of transplant recipients during this period.[2,3] To address this issue, Japan has relied on imported corneas from overseas to perform corneal transplants.[3] The Istanbul Declaration states that countries should strive to be self-sufficient in meeting their own needs, and measures should be taken to increase domestic corneal donations in Japan.[4] For many years, eye banks and awareness-raising organizations have been making various efforts to solve the problem of a shortage of corneal donations, but there has still not been a sufficient increase in corneal donations.

Potential corneal donors include patients who experience out-of-hospital cardiac arrest (OHCA) due to various conditions such as sudden cardiac arrest (SCA), acute aortic dissection (AAD) and subarachnoid hemorrhage (SAH). In Japan, approximately 120,000 people are transported to hospitals annually by ambulance due to OHCA, and most of them are taken to tertiary hospitals.[5] However, it is often difficult to achieve return of spontaneous circulation (ROSC), resulting in failure to save the lives of these patients.[5]

Criteria for corneal donation include a time limit of 6 hours from cardiac arrest to corneal donation, absence of sepsis, and no history of viral infections such as hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV). The majority of patients transported to hospitals due to OHCA may meet these criteria. In other words, patients transported to hospitals due to OHCA have the potential to be corneal donors. However, there has been no study in Japan that was carried out to clarify the patient groups and settings in which corneal donations are performed. Little is known about the association between corneal donations and settings of death (i.e., OHCA, in-hospital cardiac arrest (IHCA), and home death).

The purpose of this study was to examine the association between patients who experienced OHCA and corneal donation. We also examined the extent to which potential donors exist among different settings of death.

Materials and methods

Study design and settings

We conducted a case-control study between from January 1, 2015 to December 31, 2023 in Hiroshima Prefecture, Japan. We used data from Hiroshima Eye Bank in Hiroshima Prefecture, and from the electronic charts of Hiroshima City Hiroshima Citizens Hospital

and Fukui Internal Medicine Clinic. In 2023, Hiroshima Prefecture had a population of 2.7 million, the 11th largest in Japan, and an aging rate of 29.7%. Hiroshima City, where Hiroshima City Hiroshima Citizens Hospital and Fukui Internal Medicine Clinic are located, has a population of 1.18 million and an aging rate of 26%.[6] Hiroshima City Hiroshima Citizens Hospital, located in the center of Hiroshima City, is a tertiary care institution that receives approximately 200 cases of OHCA per year. Fukui Internal Medicine Clinic is a home care support clinic that provides palliative home care, with approximately 50 cases of death at home per year. Data from Fukui Internal Medicine Clinic were available from January 1, 2020 to December 31, 2023.

The protocol of this study was approved by the Institutional Review Board of Hiroshima City Hiroshima Citizens Hospital (approval number: 2024-35). Due to the use of anonymized data and the adoption of an opt-out approach for participant enrollment, the requirement for informed consent was waived. To report this study, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Table S1).[7]

Selection and matching of cases and controls

From the dataset of Hiroshima Eye Bank, we included all individuals who donated their corneas during the study period in Hiroshima Prefecture as cases. We did not exclude

individuals who donated their corneas under brain death or cardiac arrest. As controls, we selected potential corneal donors aged ≥10 years among all of the individuals who died in Hiroshima City Hiroshima Citizens Hospital (Hospital cohort). We defined potential corneal donors as individuals who met the criteria of corneal donation in Japan but did not donate corneas. The criteria are shown in Table S2. We matched the case group to the control group at a target ratio of 1:5.[8,9] We included age group, sex, and date of death as matching factors. Age groups were categorized as 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90-99, and 100 years of age or older. Dates of death were divided into two groups: pre-COVID-19 period (from January 2015 to December 2019) and post-COVID-19 period (from January 2020 to December 2023). We used these two groups as a matching factor.

Definition of exposure

We defined OHCA as cardiac arrest in individuals who did not occupy a hospital bed, including outpatients and visitors, and who were transported to our hospital.[10] We defined in-hospital cardiac arrest (IHCA) as cardiac arrest in individuals who occupied an inpatient hospital bed in our hospital.[10] Individuals who had ROSC after OHCA but later died after admission were included as individuals with IHCA. For individuals who donated their corneas, cases in which we could not determine whether OHCA had

occurred because private information such as information on detailed reasons for death and the names of the place where corneal donation was conducted was not available were treated as cases with missing data. Based on available data from Hiroshima Eye Bank, we categorized the subjects who donated their corneas into subjects with OHCA, those with IHCA and those who died at home or in a nursing home. In the hospital cohort, we categorized subjects who died in our hospital into subjects with OHCA and subjects with IHCA. There were no subjects who experienced OHCA in the home cohort.

Outcomes

We examined potential corneal donors in all of the subjects between different settings of death. In addition, to clarify the association between OHCA and corneal donation in Hiroshima Prefecture, we compared the proportion of subjects with OHCA in corneal donors and the proportion of subjects with OHCA in potential corneal donors.

Statistical analysis

Dichotomous variables and categorical variables were summarized using percentages. We calculated the proportion of potential corneal donors among three groups:1) subjects who experienced OHCA in our hospital, 2) subjects who experienced IHCA in our hospital, and 3) subjects who died at home under the care of Fukui Internal Medicine Clinic. We could not calculate sample size because there were no previous studies in which the

relationship between corneal donation and settings of death was investigated. All available data were therefore used for the analysis. We handled missing data under the missing at random assumption using multiple imputation. We incorporated all covariates and exposures into the imputation model. We generated 100 imputed datasets and analyzed each dataset separately using the analysis model.[11] The results from the 100 datasets were then combined using Rubin's rules to obtain the final estimates and their standard errors.[12] To compare the proportions of subjects who experienced OHCA in the case and control groups, we employed an unconditional logistic regression model.[9] We reported effect sizes as odds ratios (ORs) and 95% confidence intervals (CIs). We performed statistical analyses using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of cases and controls

We identified a total of 4877 subjects from data in Hiroshima Eye Bank, including subjects in the hospital cohort and subjects in the home cohort (Fig. 1). Table 1 shows the characteristics of subjects in the case and control groups. We included 190 subjects with corneal donation as the case group and 3394 subjects with potential corneal donation as

the control group: 3260 subjects in the hospital cohort and 134 subjects in the home cohort. During the observation period, approximately 20 subjects donated their corneas annually. In the case group, 10 subjects (5.3%) with OHCA donated their corneas, 49 subjects (26%) with IHCA donated their corneas, and 55 subjects (29%) who died at home or in a nursing home donated their corneas. In the hospital cohort of the control group, 492 subjects (15%) had OHCA and 2768 subjects (85%) had IHCA. In the home cohort, 134 subjects (100%) died at home.

Potential corneal donors in different settings of death

Fig. 2 shows the proportions of potential corneal donors in different settings of death. Of all of the identified subjects, 72% (3394) subjects were potential corneal donors. The proportion of potential donors who experienced OHCA (75%) was the highest among the different settings of death. The reasons for ineligibility for corneal donation in subjects who were not potential corneal donors are shown in Table S2.

Out-of-hospital cardiac arrest and corneal donation

Table 2 shows the relationship between OHCA and corneal donation. Based on imputed and matched data, the mean number who experienced OHCA in the corneal donation group was 26 (13%) out of 190, while the mean number of potential corneal donors who experienced OHCA was 143 (15%) out of 950. OHCA was positively associated with

corneal donation after adjustment (OR: 2.2, 95% CI: 1.3-3.5).

Discussion

Among the 4492 subjects in the hospital cohort and the 192 subjects in the home cohort, individuals who experienced OHCA or IHCA or home death were equally likely to be a potential corneal donor. Among the 190 individuals who donated corneas in Hiroshima Prefecture, the majority of individuals had IHCA or died at home. However, we found that OHCA was positively associated with corneal donation. Individuals with OHCA may be more likely than individuals with other settings of death to donate corneas.

We hypothesize two primary reasons for the observed positive association between OHCA and corneal donation. First, emergency physicians may be more aware and proactive about organ and tissue donation issues. In the 2008 Organ Donation Taskforce report, emergency physicians, as well as intensivists, are called upon to play an important role in identifying and referring dying patients who are eligible for organ donation in order to avoid losing the opportunity for donation after brain beath.[13] In other words, emergency physicians require more knowledge and experience in organ and tissue donation than do other physicians. Therefore, the results of this study may reflect the attitudes of emergency physicians toward organ and tissue donation.

Second, differences in the causes of death in individuals with OHCA and individuals with other settings of death may influence the association with corneal donation. The main causes of death in individuals with OHCA are unexpected deaths including trauma, SCA, AAD, and SAH.[14] On the other hand, most of the deaths after IHCA and deaths at home are expected to be due to terminal conditions such as malignancies. Although the feelings of donor families regarding organ donation after brain death are complex and there is no single reason to accept organ donation, organ donation is more likely to be accepted in cases of brain death due to trauma or stroke than in cases of brain death due to other causes.[15] In cases of corneal donation, the causes of death may also have a greater influence on the acceptability of the option of corneal donation for families of OHCA patients than for families of deceased patients in other settings.

OHCA may be a potential source for corneal donation in Japan. It has been reported that 70% or more of cases of non-traumatic OHCA in Japan result in death in the ED, and these deceased cases are potential corneal donors.[16] In our study, the proportion of potential corneal donors in individuals with OHCA was 75%, and the percentage in a report from an Australian ED was similar.[17] This suggests that approximately 50% of cases of OHCA have the potential for corneal donation. Considering that more than

100,000 cases of OHCA occur annually in Japan,[5] OHCA cases could be important and adequate source of corneal tissue. Targeting individuals who experienced OHCA in the ED to increase corneal donation may help to address the persistent issue of a shortage of corneas for transplantation in Japan. This approach would need a routine referral system (RRS) that presents the option of corneal donation to families of patients with OHCA in the ED. A study from the United Kingdom demonstrated that the corneal donation rate increased dramatically from 1% to 36% when such a system was implemented in the ED.[18] Similarly, the introduction of an RRS in various healthcare settings has reportedly resulted in corneal donation rates of 10-30%.[19,20] If we were to implement an RRS for families of patients with OHCA in our ED and conservatively assume a 10% donation rate, this could potentially yield 5 corneal donors per year (492 potential donors x 10% / 9 years). However, this estimated result is insufficient, considering that the number of corneal donors in Hiroshima Prefecture is about 20 per year and the corneal transplant waiting list is about 60. Therefore, the effectiveness of an RRS for OHCA cases not only in our ED but also in EDs of Hiroshima Prefecture should be examined.

Our study has several limitations that should be considered when interpreting the results. First, our case-control study utilized control data from a single tertiary hospital. This may not be fully representative of the broader population in Hiroshima Prefecture as

a whole. Our hospital has a larger number of OHCA cases than the numbers of cases in other hospitals in Hiroshima Prefecture, which may underestimate the results of our study. Second, the hospital cohort and the home cohort used to assess potential donors were also both derived from single facilities, potentially limiting the generalizability regarding our findings on proportion of potential donors. Finally, we were unable to account for all potential confounding factors that might influence the likelihood of corneal donation, such as causes of death, cultural beliefs or family dynamics. However, it was difficult to obtain this information to privacy concerns. Further prospective observational studies that can take these confounding factors into account are desirable.

Conclusion

Our study provides evidence that OHCA was positively associated with corneal donation in Hiroshima Prefecture. The observed association between OHCA and corneal donation suggests that individuals who experience OHCA may be more likely than those in other settings of death to become corneal donors. To confirm our results, a nationwide study using comprehensive data from eye banks in Japan is warranted.

Acknowledgements

We would like to appreciate Hiroshima Eye bank for providing information on corneal donation.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding information

The authors declare that they have no funding source.

Ethics statement

Approval of the research protocol with approval number and committee name: This study protocol was approved by the Institutional Review Board of Hiroshima City Hiroshima Citizens Hospital (approval number: 2024-35).

Registry and registration number of the study or trial: Not applicable

Informed Consent: Since this was a case-control study using anonymized data and an opt-out approach for participant enrollment, the requirement for informed consent was waived.

Animal Studies: Not applicable

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Table 1 Characteristics of subjects with corneal donations and potential corneal donors

	Case: corneal donation (n = 190)	Control: Potential corneal donor*	
		Hospital cohort (n = 3260)	Home cohort (n = 134)
Date (year), n (%)			
2015	23 (12)	396 (12)	-
2016	29 (15)	426 (13)	-
2017	16 (8.4)	421 (13)	-
2018	21 (11)	389 (12)	-
2019	19 (10)	331 (10)	-
2020	21 (11)	333 (10)	15 (11)
2021	18 (9.5)	320 (9.8)	31 (23)
2022	24 (13)	322 (9.9)	41 (31)
2023	19 (10)	322 (9.9)	47 (35)
Age groups (years), n (%)			
10	1 (0.5)	11 (0.34)	-
20	3 (1.6)	15 (0.46)	-
30	1 (0.5)	45 (1.4)	-
40	6 (3.2)	149 (4.6)	2 (1.5)
50	20 (11)	296 (9.1)	7 (5.2)
60	17 (8.9)	489 (15)	20 (15)
70	33 (17)	912 (28)	40 (30)
80	60 (32)	942 (29)	35 (26)
90	46 (24)	385 (12)	27 (20)
100	3 (1.6)	16 (0.49)	3 (2.2)
Male, n (%)	115 (61)	1839 (56)	32 (24)
Settings of death, n (%)			
Out-of-hospital	10 (5.3)	492 (15)	-
In-hospital	49 (26)	2768 (85)	-
Home or nursing home	55 (29)	-	134 (100) †
Missing data	76 (40)	-	-

* Potential corneal donors were defined as individuals who met the criteria of corneal donation but did not donate their corneas for some reasons.

† Individuals who died in a nursing home were not included in the home cohort of this study.

Table 2 Relationship between out-of-hospital cardiac arrest and corneal donation

	Cases: corneal donation (n = 190)	Matched controls: potential corneal donors (n = 950)	Odds ratio (95% CI) *
Out-of-hospital cardiac arrest, n (%)	26 (13) †	143 (15) †	2.2 (1.3 to 3.5)

CI, confidence interval

We matched the case group to the control group at a target ratio of 1:5 using the following matching factors: age group, sex, and date of death.

* We performed unconditional logistic regression to estimate the association between out-of-hospital cardiac arrest and corneal donation.

† The analysis was performed for each imputed dataset, and the results are presented as mean values.

Fig. 1. Subject flow chart in the case and control groups

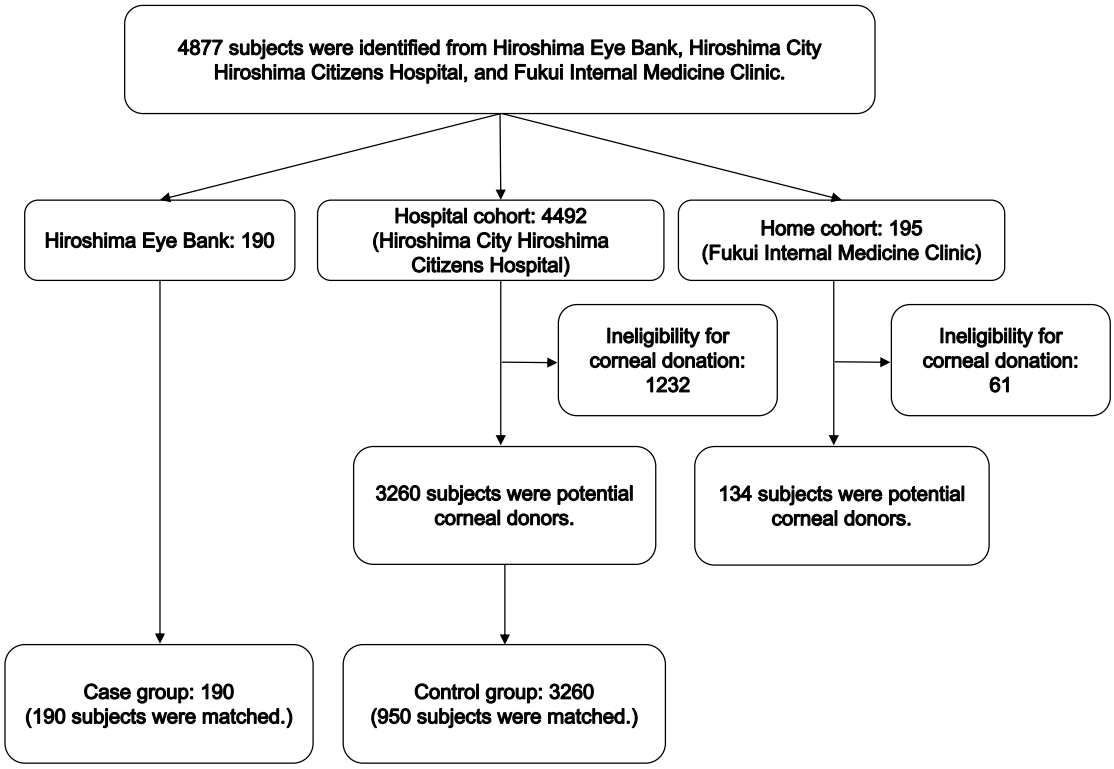
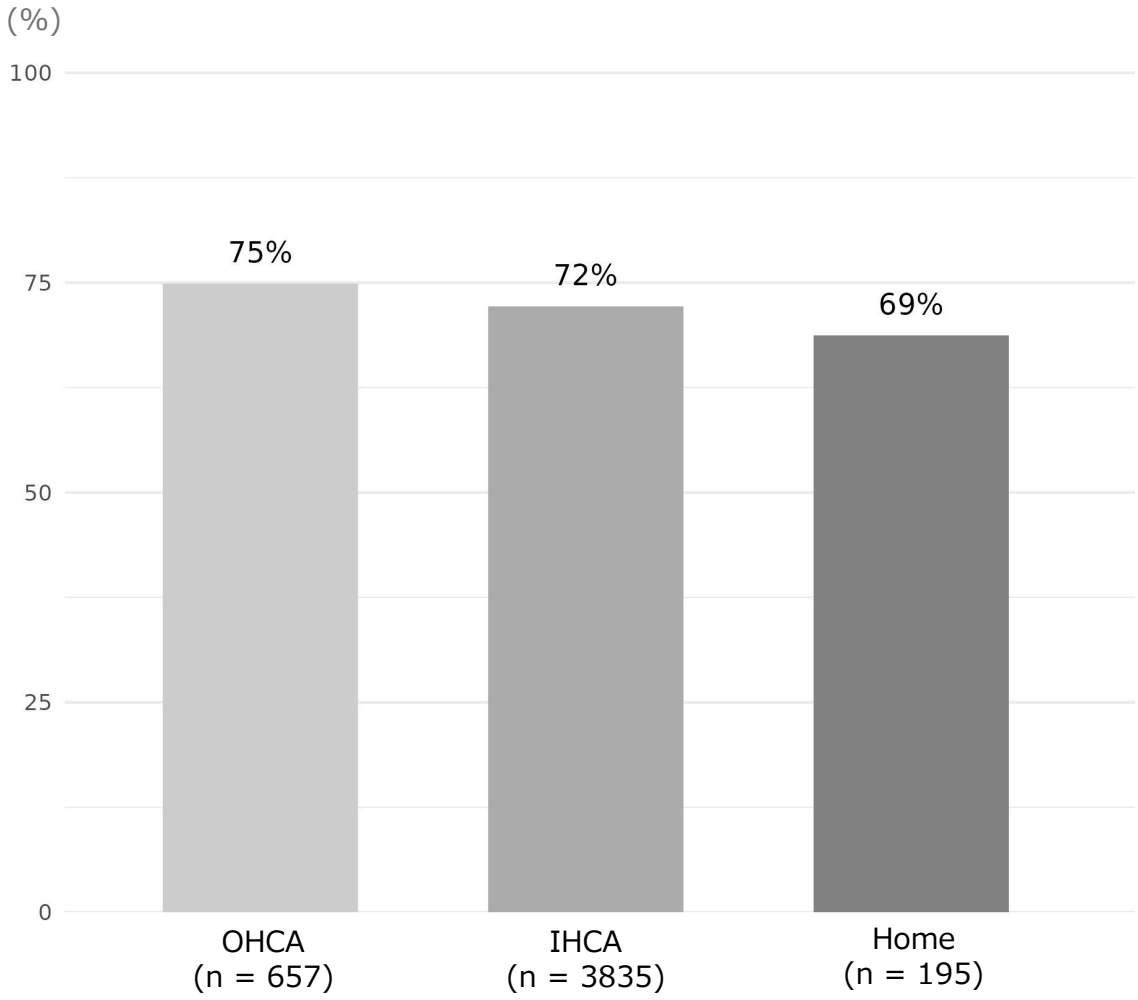


Fig. 2. Proportion of potential corneal donors in each setting of death



OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest

Individuals who experienced OHCA or IHCA were treated at Hiroshima City Hiroshima Citizens Hospital, and individuals who died at home were treated at Fukui Internal Medicine Clinic. We did not include subjects who donated corneas in each setting of death.

Supplemental material

Table S1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement - Checklist of items that should be included in reports of case-control studies

	Item No	Recommendation	Reported page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	7, 8
		(*b*) For matched studies, give matching criteria and the number of controls per case	7, 8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	9, 10
Study size	10	Explain how the study size was arrived at	9, 10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how matching of cases and controls was addressed	8
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, 11
		(b) Give reasons for non-participation at each stage	10, 11
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 11
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	11, 12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11, 12
		(*b*) Report category boundaries when continuous variables were categorized	11, 12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11, 12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14, 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13, 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls.

Table S2. Criteria for corneal donation in Japan and reasons for ineligibility of corneal donors in each setting of death

	Out-of-hospital cardiac arrest (n = 657)	In-hospital cardiac arrest (n = 3835)	Home death (n = 195)
Ineligibility of corneal donors, n (%)	165 (25)	1067 (28)	61 (31)
Reasons for ineligibility of corneal donors, n (%)			
More than 6 hours having passed since death	101 (61)	1 (0.1)	12 (20)
Unknown cause of death	-	4 (0.4)	-
Active viral encephalitis	-	1 (0.1)	-
Delayed-onset viral encephalitis*	-	-	-
Systemic infections (e.g., bacteria, viruses, or fungi)†	41 (25)	721 (68)	38 (62)
HIV antibody, HTLV-1 antibody, HBs antigen, or HCV antibody-positive	21 (29)	225 (21)	8 (13)
Creutzfeldt-Jakob disease	-	-	-
Leukemia, malignant lymphoma	2 (1.2)	114 (11)	2 (3.3)
Reye's syndrome	-	-	-
Orbital tumor	-	1 (0.1)	1 (1.6)

HIV, human immunodeficiency virus; HTLV-1, human T-lymphotropic virus type 1; HBs, hepatitis B surface; HCV, hepatitis C virus

* Subacute sclerosing panencephalitis and progressive multifocal leukoencephalopathy were included.

† We included coronavirus infection disease that emerged in 2019 (COVID-19).