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ORIGINAL RESEARCH

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One-year survival after out-of- hospital cardiac arrest: Sex-based survival analysis in a Canadian population

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Abstract

Objective: We investigated sex differences in 1-year survival in a cohort of patients who survived out-of-hospital cardiac arrest (OHCA) to hospital discharge. We hypothesized that female sex is associated with higher 1-year posthospital discharge survival.

Methods: A retrospective analysis of linked data (2011–2017) from clinical databases in British Columbia (BC) was conducted. We used Kaplan–Meier curves, stratified by sex, to display survival up to 1-year, and the log-rank test to test for significant sex differences. This was followed by multivariable Cox proportional hazards analysis to investigate the association between sex and 1-year mortality. The multivariable analysis adjusted for variables known to be associated with survival, including variables related to OHCA characteristics, comorbidities, medical diagnoses, and in-hospital interventions.

Results: We included 1278 hospital-discharge survivors; 284 (22.2%) were female. Females had a lower proportion of OHCA occurring in public locations (25.7% vs. 44.0%, $P < 0.001$), a lower proportion with a shockable rhythm (57.7% vs. 77.4%, $P < 0.001$), and fewer hospital-based acute coronary diagnoses and interventions. One-year survival for females and males was 90.5% and 92.4%, respectively (log-rank $P = 0.31$). Unadjusted (hazard ratio [HR] males vs. females 0.80, 95% confidence interval [CI] 0.51–1.24, $P = 0.31$) and adjusted (HR males vs. females 1.14, 95% CI 0.72–1.81, $P = 0.57$) models did not detect differences in 1-year survival by sex.

Conclusion: Females have relatively unfavorable prehospital characteristics in OHCA and fewer hospital-based acute coronary diagnoses and interventions. However, among survivors to hospital discharge, we found no significant difference between males and females in 1-year survival, even after adjustment.

KEYWORDS

cardiac arrest, sex, survival

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1 | INTRODUCTION

1.1 | Background

Out-of-hospital cardiac arrest (OHCA) is a major health concern worldwide, with an adult incidence rate of 55 per 100,000 person-years.[1] Previous studies examining sex differences in OHCA reported significant imbalance in baseline characteristics predictive of OHCA outcomes, with females having a lower proportion with witnessed arrest, bystander cardiopulmonary resuscitation (CPR), and initial shockable rhythms.[2–6] Reports from other studies demonstrated significant differences in prehospital treatments, with females less likely to receive bystander CPR and defibrillation,[7] recommended resuscitation interventions, and medications[8,9] and less likely to be transported to hospital before achieving return of spontaneous circulation, compared to males.[5] Previous analyses have demonstrated that, after adjustment for baseline characteristics and prehospital interventions, females had equal or higher probability of short-term survival (survival to hospital discharge or 30 days survival) compared to males.[2,10–13] Most previous studies of sex-based disparities in OHCA outcomes adjusted for only prehospital cardiac arrest characteristics and treatment variables while largely neglecting comorbid conditions, possibly leaving a large proportion of variation in outcomes unexplained. Furthermore, these studies investigated short-term survival, specifically survival to hospital discharge[2,11,14,15] and 1-month survival.[10,11,13] Research about sex differences in long-term survival and survival beyond hospital discharge is still scant.

1.2 | Importance

This study addresses sex differences in OHCA long-term survival and sets the stage for future investigations into postresuscitation interventions and outcomes. The findings of this study fill a gap in OHCA long-term survival research and provide guidance to health care professionals and policymakers with the ultimate goal of improving resuscitation and postresuscitation interventions and long-term survival outcomes for both males and females.

1.3 | Goal of this investigation

The primary objective of this study was to investigate sex differences in 1-year survival in a cohort of patients who survived OHCA to hospital discharge. We hypothesized that female sex is associated with higher 1-year survival posthospital discharge, after adjustment for baseline differences.

2 | METHODS

2.1 | Study design and setting

First, we used the British Columbia (BC) Cardiac Arrest Registry to identify patients who suffered OHCA (2011–2017). The BC Cardiac Arrest Registry prospectively identifies and collects data on emergency medical system (EMS)-assessed non-traumatic OHCA, including characteristics, bystander interventions, treating EMS-units, time-stamped EMS treatments provided, including administration of drugs, advanced airway placement, transport to hospital, and prehospital outcomes. Second, Population Data BC, a provincial administrative data steward, linked the BC Cardiac Arrest Registry data to administrative and clinical databases in BC including BC Vital Statistics, Cardiac Services BC, and the BC Discharge Abstracts Database (DAD). DAD includes detailed information on hospital date of admission, date of discharge, status at discharge (alive vs dead), comorbidities, and most responsible admission diagnoses. Most responsible diagnoses were determined as the diagnosis of acute care hospitalizations after OHCA. Fordyce et al. provide detailed description of the data sources and linkage.[16] The Cardiac Services BC HEART Information System provided data on cardiac interventions and outcomes. BC Vital Statistics provided information on all deaths, including date and location of death.

The Bottom Line

In this retrospective study, female and male cardiac arrest patients who survived to hospital discharge had similar 1-year survival after adjusting for several important variables.

2.2 | Study population

In the analytic data set, we examined cases from the BC Cardiac Arrest Registry and included adult (age ≥18 years) EMS-treated OHCAs that survived to hospital discharge. We excluded cases for whom linkages were unsuccessful, or cases missing data on sex or other variables required for analysis.

2.3 | Measures

The independent variable was sex (male and female). Sex data were obtained from hospital records. The primary outcome of interest was 1-year mortality. One-year mortality was defined as death from any cause within 1 year from date of hospital discharge. The secondary outcome was time to death.

2.4 | Statistical analysis

2.4.1 | Univariate and bivariate analysis

We calculated summary statistics for each baseline characteristic. Continuous variables were presented as means and SDs, if normally distributed, or otherwise as medians and interquartile ranges.

Categorical variables were presented as counts and percentages. Bivariate analyses were performed using Student's *t* test or Mann-Whitney *U*-test (as appropriate) for continuous variables and chi-square test for categorical variables, to examine the association between baseline characteristics and sex. One-year mortality was calculated and presented as crude rates, counts per 1000-person years, to account for differences in follow-up time. Kaplan–Meier curves, stratified by sex, were used to display survival duration, and the log-rank test was used to test for significant differences between males and females.

2.4.2 | Multivariable analysis

We used Cox proportional hazards regression to investigate the independent association between sex and 1-year mortality. For each subject, observation began on the date of hospital discharge and continued up to 1 year or until death or censoring. The primary end point was all-cause mortality.

We began the multivariable analysis by conducting a preliminary evaluation of the significance and effect sizes of all potential explanatory variables including (1) OHCA characteristics and prehospital treatment variables–dispatch to EMS arrival time interval, location of arrest (public vs private), witness status (witnessed vs not witnessed), bystander CPR, initial cardiac rhythm (shockable vs non-shockable), administration of epinephrine; (2) comorbidities–patients' medical history within 3 years before OHCA, including history of hypertension, diabetes mellitus (DM), congestive heart failure, coronary artery disease (CAD), chronic kidney disease, and cancer; (3) in-hospital most responsible diagnoses–ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and cardiogenic shock; and (4) in-hospital interventions-percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), pacemaker implant, implantable cardioverter defibrillator (ICD).

By conducting this preliminary evaluation, we identified the explanatory variables that are significantly associated with the outcomes and determined their effect sizes. We used both a statistical approach and a theory-guided approach to determine the order in which explanatory variables will be entered in the model, using a 5-step forward variable selection process. In step 1, we examined the crude hazard ratio (HR) of sex by including sex only in the Cox regression model. After step 1, we added explanatory variables based on their clinical relevance, statistical significance, and effect sizes. Variables with the largest effect sizes were entered first, followed by those with smaller effect sizes. In step 2, we included sex along with OHCA characteristics and prehospital treatment variables. In step 3, we added comorbidities to the model. In step 4, we added medical diagnosis covariates, and in step 5, we added in-hospital interventions. Finally, we tested an interaction term, including age and sex, to include in the models if statistically significant.

Before multivariable analyses, we examined the proportional hazard assumption by assessing whether the HR was constant over time. This was done by visualization of log minus log survival versus log time graph and by examining the interactions between all covariates with time.[17] All analyses were performed using IBM SPSS version 26 (Armonk, New York, USA). Ethics approval for this study was obtained from the affiliated University of British Columbia—Providence Health Care Research Ethics Board.

3 | RESULTS

3.1 | Baseline characteristics and univariate analyses

There were 9982 (2904 [29.1%] females and 7078 [70.9%] males), EMS-treated OHCAs in the study footprint. Out of these cases, 1325 patients survived to hospital discharge, comprising 295 (22.3%) females and 1030 (77.7%) males. The proportion of female survivors was significantly lower than that of males (10.2% [295/2904] vs 14.5% [1030/7078]) ($P < 0.001$) (Figure 1).

After excluding 47 cases (3.5%) due to missing data on covariates required for analysis (Figure 1), a total of 1278 hospital-discharge survivors were included in the analytic data set. Among them, 284 (22.2%) were females, 510 (40.0%) experienced cardiac arrest in public locations, 933 (73.0%) had shockable initial rhythms, 677 (53.0%) had a history of hypertension, and 322 (25.2%) had a history of DM. Table 1 provides the summary statistics for baseline characteristics, OHCA treatment, and comorbidities, both overall and stratified by sex.

The female-male comparison showed that females had a lower proportion of OHCA occurring in public locations (25.7% vs 44.0%, $P < 0.001$) and a lower proportion with a shockable initial rhythm (57.7% vs 77.4%, $P < 0.001$). In comparing medical history, no significant differences were detected between males and females except that the proportion of females with prior identified CAD was lower than the proportion of males (29.6% vs 56.6%, $P < 0.001$). Females had a lower proportion of acute STEMI on admission than males (18.3% vs 34.0%, $P < 0.001$), and the proportion of females who had in-hospital cardiac interventions, either PCI or CABG, was significantly lower than the proportion of males. Specifically, females had fewer PCIs and fewer CABG surgeries (26.1% vs 39.6, $P < 0.001$ and 1.8% vs 12.3%, $P < 0.001$, respectively). ICDs were implanted in 25% of patients; 22.2% of females and 25.7% of males, $P = 0.22$ (Table 1).

3.2 | Survival analysis

Overall, 91.9% of cases survived until 1 year. We did not detect a difference in 1-year survival between females (90.5%) and males (92.4%). Figure 2 shows the Kaplan–Meier curve of survivors up to 12 months after hospital discharge; the log-rank test was not significant ($P = 0.31$). The calculated overall mortality rate was 81 per 1000-person years. The sex-specific mortality was higher in females (95 per 1000-person years) compared to males (76 per 1000-person years).

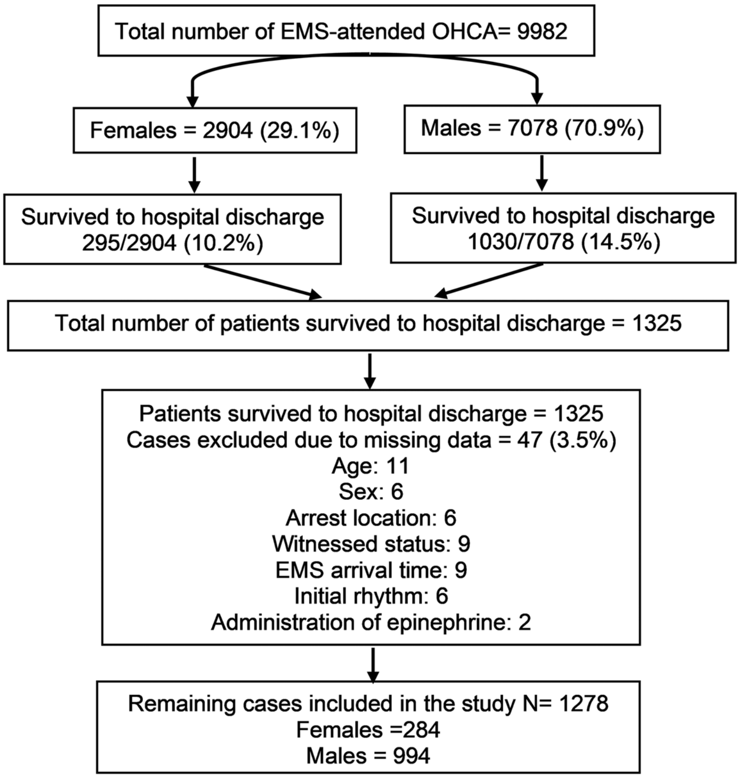

FIGURE 1 Study flow diagram. Abbreviations: EMS, emergency medical services; OHCA, out-of-hospital cardiac arrest.

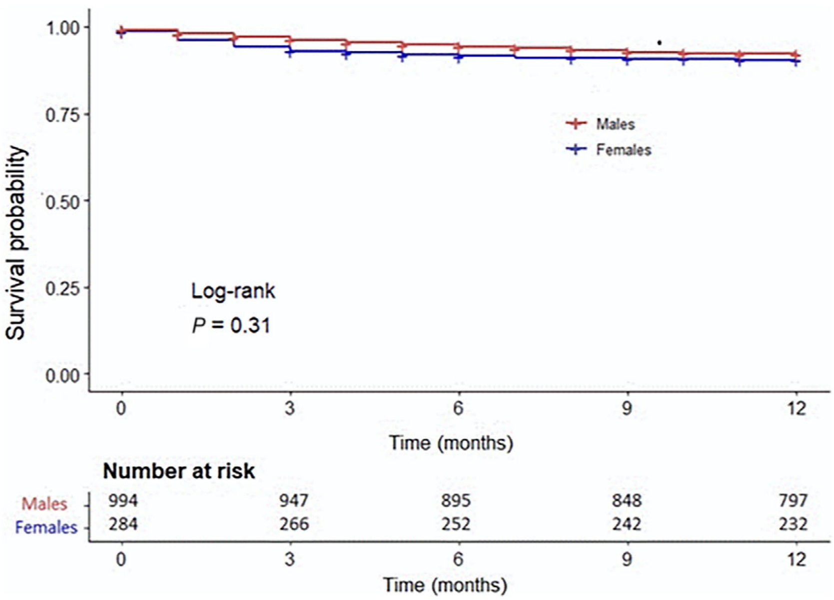

FIGURE 2 Kaplan–Meier survival estimates for females and males.

3.3 | Multivariable model

Visual inspection of the covariates' log minus log survival curves showed the curves were parallel. There were no significant interactions between any covariates and time, indicating the proportional hazards assumption was not violated.

Table 2 shows the unadjusted and adjusted Cox regression analysis results. The unadjusted analysis showed no association between sex and risk of death (crude HR males vs females 0.80, 95% confidence interval [CI] 0.51–1.24, P = 0.31). After adjusting for OHCA characteristics, the analysis continued to show no association between sex and hazard of death (HR males vs females 1.02, 95% CI 0.51–1.73, $P = 0.78$) (Model 2). The association between sex and 1-year mortality remained insignificant after adding comorbidities and most responsible diagnoses to the model (Model 3 and 4). The final model, which included covariates related to OHCA characteristics, comorbidities, most responsible diagnoses, and in-hospital interventions, demonstrated no sex difference either (HR males vs females 1.14, 95% CI 0.72–1.81, $P = 0.57$) (Model 5). The final model includes covariates that varied significantly by sex or had statistically significant effect on the outcome or they are known to be clinically important. We tested the interaction term (age × sex) in the final model. The age × sex interaction

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TABLE 1 Sex differences in baseline characteristics, comorbidities, and intervention.

Variables	Total *N* = 1278	Females *n* = 284 (22.2%)	Males *n* = 994 (77.8%)	*P* value
Age, year (mean ± SD)	61.0 ± 15.3	66.0 ± 16.7	61.0 ± 14.9	0.22
OHCA characteristics				
Time to EMS arrival, minute (median IQR)	8.1 (6.5–11.5)	9.5 (7.1–13.2)	8.19 (6.4–11.0)	<0.001
Arrest in public location	510 (40.0%)	73 (25.7%)	437 (44.0%)	<0.001
Unwitnessed	233 (18.2%)	60 (21.1%)	173 (17.4%)	
Bystander witnessed	249 (19.5%)	78 (27.5%)	171 (17.2%)	
EMS witnessed arrest	796 (62.3%)	146 (51.4%)	650 (65.4%)	<0.001
No bystander CPR	246 (19.2%)	69 (24.3%)	177 (17.8%)	
First CPR by bystander[a]	237 (18.5%)	70 (24.6%)	167 (16.8%)	
First CPR by EMS[b]	795 (62.3%)	145 (51.1%)	650 (65.4%)	<0.001
Shockable initial rhythm	933 (73.0%)	164 (57.7%)	769 (77.4%)	<0.001
Administration of epinephrine	497 (38.9%)	92 (32.4%)	405 (40.7%)	0.01
Comorbidities				
Hypertension	677 (53.0%)	139 (48.9%)	538 (54.1%)	0.12
Diabetes mellitus	322 (25.2%)	71 (25.0%)	251 (25.3%)	0.93
Congestive heart failure	183 (14.3%)	40 (14.1%)	143 (14.4%)	0.89
Coronary artery disease	647 (50.6%)	84 (29.6%)	563 (56.6%)	<0.001
Chronic kidney disease	254 (19.9%)	47 (16.5%)	207 (20.8%)	0.11
Cancer	72 (5.6%)	12 (4.2%)	60 (6.0%)	0.24
Most responsible diagnosis				
Others (non-MI)	818 (64.0%)	222 (78.2)	596 (60.0%)	
STEMI	390 (30.5%)	52 (18.3%)	338 (34.0%)	<0.001
NSTEMI	70 (5.5%)	10 (3.5%)	60 (6.0%)	
In-hospital interventions				
Diagnostic angiography	886 (69.3%)	150 (52.8%)	736 (74.0%)	<0.001
No revascularization	683 (53.4%)	205 (72.2%)	478 (48.1%)	
PCI	468 (36.6%)	74 (26.1%)	394 (39.6%)	<0.001
CABG	127 (10.0%)	5 (1.8%)	122 (12.3%)	
Pacemaker implant	88 (6.9%)	20 (7.0%)	68 (6.8%)	0.90
ICD implant	319 (25.0%)	63 (22.2%)	256 (25.8%)	0.22
Survival outcomes				
One-year survival	1174 (91.9%)	257 (90.5%)	918 (92.4%)	0.31

Abbreviations: CABG, coronary artery bypass graft surgery; CPR, cardiopulmonary resuscitation; EMS, emergency medical system; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
[a]Witnessed by bystander, and first CPR was initiated by bystander while waiting for EMS.
[b]Witnessed by EMS, and first CPR was initiated by EMS.

was not statistically significant (HR 0.99, 95% CI 0.96–1.04, $P = 0.91$); therefore, it was not included in the model.

4 | LIMITATIONS

This study has a number of limitations. First, the results may not be generalizable to other regions where there are differences in prehospital EMS intervention and postarrest in-hospital care. However, we applied our study questions/hypothesis to a North American province where OHCA cases are served by a single, unified provincial EMS. Second, the result may be not generalizable to all OHCA patients as we included OHCAs who were discharged from hospital alive. The rationale for not including those with failed prehospital resuscitation and those who died in hospital in our analysis is that those patients had no chance to be exposed to some in-hospital treatments, such

TABLE 2 Effect of sex on 1-year mortality.

Model	HR[a]	(95% CI)	*P* value	Variable included
Model 1	0.80	0.51–1.24	0.31	Sex only
Model 2	1.02	0.57–1.72	0.78	Sex, age, and OHCA characteristics (arrest location, witnessed status, initial rhythm)
Model 3	1.09	0.67–1.73	0.70	Model 2 plus: comorbidities (CAD, CHF, CKD, and cancer)
Model 4	1.09	0.69–1.73	0.72	Model 3 plus: most responsible diagnosis (STEMI and NSTEMI).
Model 5	1.14	0.72–1.81	0.57	Model 4 plus: in-hospital interventions (ICD implant, PCI, and CABG)

Note: Effect of sex on 1-year mortality adjusting for OHCA characteristics, comorbidities, hospital diagnoses, and interventions.
Abbreviations: CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; ICD, implantable cardioverter defibrillator; NSTEMI, non-ST-segment elevation myocardial infarction; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
[a]Hazard ratios (males vs females).

as PCI and CABG (or in-hospital treatments were nor indicated for them due to poor prognosis—for those who died in hospital). Including those patients in the analysis, which adjusted for in-hospital treatments variables, would produce inaccurate estimates of not only the significance but also the magnitude of the relationships between the explanatory and outcome variables. Nevertheless, patients surviving the hospital discharge after OHCA remain an important subgroup with recent emphasis on survivorship.[18] Lastly, in survival analysis, loss of follow-up can potentially introduce bias in point estimation, particularly when a large proportion of patients are lost, and if they systematically differ from those who remain in the study.[19] However, in our study, only 23 patients (13 males and 10 females) were lost to follow-up, and we had no information regarding their status or outcomes.

5 | DISCUSSION

In this cohort of EMS-treated OHCA subjects, who survived to hospital discharge, females tended to have relatively unfavorable prehospital characteristics and fewer hospital-based acute coronary diagnoses and interventions. However, unadjusted and adjusted analysis revealed no significant difference in 1-year survival. To our knowledge, this is the first study examining the effect of sex on 1-year survival that adjusted for prehospital treatment, comorbidities, admission diagnoses, and in-hospital interventions. The results add to our knowledge of sex-based differences in long-term OHCA outcomes.

It is important to note that initially, among OHCAs in the study footprint for whom linkages were successful, the proportion of female survivors until hospital discharge was lower compared to males. This finding is consistent with other studies that have reported a disadvantage in crude survival to hospital discharge among females.[6,20,21] This disadvantage might be explained by the unfavorable baseline characteristics of females. Interestingly, despite the unfavorable baseline characteristics of females, our data demonstrated no significant sex difference in 1-year survival. The reason for this observation is unclear, but one possibility is the impact of female sex hormones. Previous studies have suggested that these hormones may have a positive impact on resuscitation outcomes.[14] Therefore, female sex hormones might have improved 1-year survival in females.

Previous analyses examining long-term survival have reported results similar to ours. Andrew et al.[22] did not detect any association between sex and 1-year survival (male HR 1.17, 95% CI 0.97–1.40, $P = 0.09$). Chan et al.[23] reported no difference in 1-year mortality by sex (female HR 1.03, 95% CI 0.82–1.31, $P = 0.79$). In contrast to our study, Chan et al. and Andrew et al. did not adjust for in-hospital treatment variables in their analysis. Nevertheless, all 3 studies found no association between sex and 1-year survival. The consistency of these results, despite the variation in analytic techniques, supports the validity of our findings.

Females have relatively unfavorable prehospital characteristics in OHCA and fewer hospital-based acute coronary diagnoses and interventions. However, we found no significant difference between males and females in 1-year survival. This is one of the first studies examining the effect of sex on postdischarge survival that adjusted for more confounders, including prehospital treatment, comorbidities, admission diagnoses, and in-hospital interventions. This study adds to our knowledge of sex-based differences in long-term OHCA outcomes.

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AUTHOR CONTRIBUTIONS

Emad Awad, Jim Christenson, Christopher B. Fordyce, and Karin Humphries conceived the study concepts and design. Jim Christenson, Christopher B. Fordyce, Jennie Helmer, and Brian Grunau provided advice on design and statistical analysis. Emad Awad and Karin Humphries analyzed the data and interpreted the results. All authors revised the articles for important intellectual contents. All authors reviewed the results and approved the final version of the manuscript. Emad Awad takes responsibility for the paper as a whole.

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