CJC Open 7 (2025) 449–455

Original Article

Factors Associated With Withdrawal of Life-Sustaining Therapy After Out-of-Hospital Cardiac Arrest

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ABSTRACT

Background: Out-of-hospital cardiac arrest (OHCA) is a leading cause of global mortality. Most patients get hypoxic brain injury, which often leads to the withdrawal of life-sustaining therapy (WLST) because of concerns of poor neurologic prognosis. This study describes the rates and reasons for WLST and identifies factors associated with early WLST, defined as occurring within 72 hours of admission.

Methods: We conducted a multicentered, retrospective cohort study of adult OHCA patients admitted to 3 large academic hospitals in Toronto from January 2012 to December 2019. Data were extracted from medical records and analyzed using descriptive statistics and cause-specific hazards regression models to identify factors associated with WLST and documented goals of care (GOC) discussions.

Results: Among 264 patients (median age 66 years, 76.5% male), the in-hospital mortality rate was 62.1%. Of the nonsurvivors, 67.1% died following WLST (90% of cases because of concern of poor neurologic prognosis), with 50% of WLST occurring <72 hours from admission. Formal declaration of brain death only occurred 9.8% of the time. Older age significantly increased the risk of early WLST. GOC discussions were documented only 56.4% of the time in the overall cohort and significantly associated with WLST across all time periods.

RÉSUMÉ

Contexte : Les arrêts cardiaques survenant hors de l'hôpital sont une des principales causes de mortalité dans le monde. Dans la plupart des cas, les patients subissent des lésions cérébrales hypoxiques, ce qui mène souvent à l'arrêt du traitement de maintien des fonctions vitales (AMFV) en raison d'un pronostic neurologique sombre. Cette étude décrit la fréquence et les motifs de l'AMFV et détermine les facteurs associés à l'AMFV précoce, défini comme survenant dans les 72 heures suivant l'admission à l'hôpital.

Méthodologie : Nous avons mené une étude de cohorte rétrospective multicentrique chez des adultes ayant subi un arrêt cardiaque à l'extérieur de l'hôpital qui ont été admis dans trois grands hôpitaux universitaires de Toronto entre janvier 2012 et décembre 2019. Les données proviennent de dossiers médicaux et ont été analysées au moyen de statistiques descriptives et de modèles de régression des risques par cause afin de déterminer les facteurs associés à l'AMFV et les discussions documentées sur les objectifs thérapeutiques.

Résultats : Parmi 264 patients (âge médian : 66 ans; 76,5 % d'hommes), le taux de mortalité à l'hôpital était de 62,1 %. Parmi ceux qui n'ont pas survécu, 67,1 % sont décédés après un AMFV (90 % en raison du pronostic neurologique sombre), 50 % des AMFV étant sur-

Out-of-hospital cardiac arrest (OHCA) describes the sudden cessation of cardiac mechanical activity and circulatory collapse outside of a hospital setting, originating from various etiologies.[1] Despite significant advances in resuscitation science, OHCA continues to be a leading cause of global mortality, with about 10% of patients surviving to hospital discharge.[2,3] Among the approximately 25% of patients admitted alive to hospital after OHCA, many have to deal with the effects of hypoxic brain

Received for publication August 13, 2024. Accepted November 14, 2024.

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See page 455 for disclosure information.

https://doi.org/10.1016/j.cjco.2024.11.013

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Conclusions: This study highlights the high incidence of WLST, and specifically early WLST, in OHCA patients. GOC discussions are routinely undocumented and is associated with a higher likelihood of WLST. These findings underscore heterogeneity of practice, and the influence of GOC discussions in education and shared decision making.

venus moins de 72 heures après l'admission. Il y a eu une déclaration de mort cérébrale seulement dans 9,8 % des cas. L'âge avancé augmente considérablement le risque d'AMFV précoce. Les discussions sur l'objectif thérapeutique ont été documentées dans seulement 56,4 % des cas dans la cohorte globale et ont été grandement associées à un AMFV à toutes les périodes de temps.

Conclusions : Cette étude souligne la fréquence élevée des AMFV, et particulièrement des AMFV précoces, chez les patients subissant un arrêt cardiaque hors de l'hôpital. Les discussions sur les objectifs thérapeutiques ne sont habituellement pas documentées et sont associées à une probabilité accrue d'AMFV. Ces observations soulignent l'hétérogénéité de la pratique et l'influence des discussions sur l'objectif thérapeutique dans l'éducation et la prise de décision conjointe.

injury and related complications of poor end-organ perfusion.[4] Most patients who are admitted to hospital are critically ill, and accurately predicting neurologic outcomes can be challenging. The most common mode of death in these patients is death following the withdrawal of life-sustaining treatment (WLST) for presumed poor neurologic prognosis, occurring in 59% of cases.[5] In contrast, formal declaration of brain death accounts for only 11% of cases.[6]

Guidelines have been established to prevent premature WLST before accurate neurologic prognostication can be performed. Although exceptions exist, a critical recommendation is that definitive conclusions about neurologic prognosis should generally not be drawn earlier than 72 hours after cardiac arrest, because of the limited accuracy of clinical examination and imaging tests during that period.[7,8] These considerations are especially important when sedation is provided as part of targeted temperature management after the arrest, which can further complicate prognostic assessment.[9,10] Early WLST—defined as withdrawal of life support within 72 hours of cardiac arrest—has been previously shown to occur in up to a third of patients without extracorporeal cardiopulmonary resuscitation (CPR).[6,11-13] Family—medical team dynamics and goals of care (GOC) discussions are thought to play an integral role in determining early WLST.[14] These discussions are often complex and multifaceted, with age, sex, race, preexisting comorbid status, poor neurologic status at the time of admission, and cardiac arrest characteristics all playing a role.[15]

The primary objective of this study was to describe rates of WLST and documented reasons for death among nonsurvivors following OHCA, in a large university academic hospital environment. Secondary objectives included describing the characteristics of individuals who receive WLST within 72 hours after admission, and the clinical factors associated with the timing of WLST. We also sought to examine prevalence and timing of documented GOC discussions to better understand the impact of these conversations on patients' care trajectories.

Methods

Study design and setting

We conducted a multicenter, retrospective cohort study involving adult patients (≥18 years) with nontraumatic OHCA admitted to and/or transferred alive to 3 large academic teaching hospitals affiliated with the University of Toronto: Unity Health (St. Michael's Hospital), Sunnybrook Health Sciences Centre, and University Health Network (Toronto General Hospital [TGH]) between January 2012 and December 31, 2019. Data abstraction from the patients' medical records was completed by trained abstractors. The medical records were reviewed, and data abstracted to describe prehospital and emergency medical services resuscitation metrics, as well as in-hospital clinical data until death or discharge. Exclusion criteria included pre-existing "No CPR" orders, OHCA due to traumatic causes, or invalid or missing health card number. The study and data collection were approved by the research ethics board at each participating hospital.

A chart review using all available documentation in the hospital patient record (ie, Soarian Clinicals electronic patient record [EPR] at St. Michael's Hospital, SunnyCare and MetaVision at Sunnybrook Health Sciences Centre, EPR at Toronto General Hospital) was performed to extract data related to (1) baseline demographics: age and sex, date of admission, date of death, discharge, or transfer; (2) arrest information; (3) pre-existing medical comorbidities; (4) in-hospital investigations, interventions, and procedures related to the OHCA; (5) medical comorbidities that developed in hospital as a consequence of the OHCA; (6) neurologic trajectory; (7) GOC discussions; and (8) WLST or cause of death. Cases for which documentation was unclear or ambiguous for specific data points were reviewed collectively, and consensus was reached to ensure accurate and consistent data collection. The Supplemental Appendix S1 lists specific information abstracted from the patient records.

We defined WLST as the cessation of life support leading to death, without formal declaration of brain death. Brain death was defined as a declaration in the medical record that the patient has been deemed to satisfy criteria for neurologic determination of death.[16] Death while receiving life-sustaining therapy was defined as an acute deterioration secondary to non-neurologic complications and leading to death despite life support, with no CPR performed. Death with CPR was declared when a patient did not survive an active CPR effort. A GOC discussion was counted as having occurred if there was a unique chart entry documenting a conversation with any substitute decision makers regarding

Table 1. Baseline characteristics and clinical characteristics of patients following OHCA admitted to hospital comparing survivors and nonsurvivors

Baseline characteristic	Survivors (n = 100)		Nonsurvivors (n = 164)	
	n	Median (IQR) or n (%)	n	Median (IQR) or n (%)
Age, y	100	62 (53-71)	164	69 (57-80)
Male sex	100	85 (85)	164	117 (71)
BMI	69	27 (24-29)	75	27 (23-30)
EMS response time, min	56	4 (3-6)	86	5 (3-7)
Bystander CPR	66	47 (71)	108	60 (56)
Shockable rhythm, VT/VF	69	54 (78)	104	26 (25)
Days in hospital	100	12 (6-24)	164	3 (1-8)
No cardiac risk factors	93	34 (37)	139	31 (22)
Previous episode of VT/VF	95	2 (2.1)	141	0 (0)
Initial laboratory values				
Creatinine	89	112 (92-136)	151	122 (95-168)
Lactate	83	2.7 (1.0-7.28)	154	7.8 (1.4-11.5)
Initial ECG ST elevation	97	26 (27)	157	24 (15)
Invasive mechanical ventilation	100	73 (73)	164	158 (96)
TTM	100	54 (54)	164	99 (60)

All characteristics are represented by median (IQR) or number (percentage). TTM was always completed for 24 hours as per local protocol. "No cardiac risk factors" was defined as the absence of hypertension, dyslipidemia, coronary artery disease, diabetes mellitus, and obesity.

BMI, body mass index; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; EMS, emergency medical services; OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management; VT, ventricular tachycardia; VF, ventricular fibrillation.

prognosis, patient values, neuroprognostication, or the appropriateness of CPR. Other clinical notes with substantive documentation of these elements were reviewed on a case-by-case basis to ensure consistency and accuracy in capturing all relevant discussions. Substitute decision makers were appointed according to the Ontario Health Care Consent Act, which included the Public Guardian and Trustee if no representative was immediately available.[17]

Statistical analyses

Clinical characteristics were summarized using descriptive statistics. Continuous variables were characterized using median and the first/third quartiles; dichotomous or polytomous categorical variables were characterized using frequencies. We also described the clinical characteristics of all patients, stratifying them by survivors and nonsurvivors. To address the primary objective, the outcome considered in the analyses was in-hospital death, in particular death following WLST. We characterized this outcome using both descriptive statistics and Fine and Gray's subdistribution methods in terms of cumulative proportion of deceased patients, overall and by the mode of death.

Next, we applied separate cause-specific hazards regression models to quantify clinical factors at admission associated with the GOC and with death after WLST. In this analysis, we considered patients' sex and age at admission, body mass index, calculated EMS response time, the presence of bystander CPR, initial lactate, and arrest rhythm. EMS response time, bystander CPR, and initial rhythm were considered as proxies for optimal resuscitation conditions.[18] The association of continuous factors (eg, age) were quantified using natural cubic splines, and the results were shown graphically on a log hazard scale. The association of other categorical variables were quantified using hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) based on Wald statistics. In addition, we assessed and quantified the association of the aforementioned clinical factors with death following WLST within or after 72 hours of admission.

Given that documented GOC discussions could take place anytime between admission and discharge/death, we considered the discussion as a time-dependent variable. We first characterized the incidence of documented GOC discussions using Fine and Gray's subdistribution method with hospital

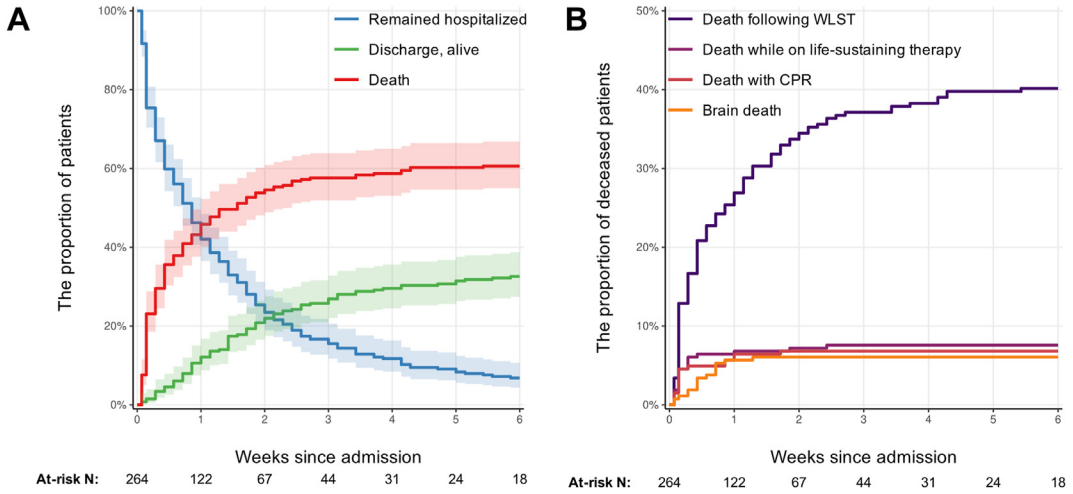

Figure 1. (**A**) The cumulative proportion of patients discharged alive, dead, or remaining hospitalized, summarized using the Fine-Gray subdistribution method. (**B**) The proportion of deceased patients (as a proportion of all patients) broken down by modes of death. CPR, cardiopulmonary resuscitation; WLST, withdrawal of life-sustaining therapy.

Table 2. The results of cause-specific hazard regression summarized for WLST <72 hours

Variable	HR (95% CI)	*P* value
Age, y	Nonlinear (Fig. 2)	0.002
Female, vs male	1.405 (0.708, 2.788)	0.32
Calculated EMS response time, min	Nonlinear (Fig. 2)	0.89
Initial lactate, mmol/L	Nonlinear (Fig. 2)	0.117
BMI, vs normal		0.87
Obese	0.988 (0.395, 2.474)	
Overweight	0.819 (0.301, 2.227)	
Underweight	1.465 (0.322, 6.668)	
Bystander CPR administration, vs no CPR	0.799 (0.357, 1.787)	0.57
Initial arrest rhythm		0.40
Asystole	2.161 (0.843, 5.535)	
PEA	1.442 (0.581, 3.580)	
Shockable rhythm, VT or VF	1.090 (0.306, 3.881)	

BMI, body mass index; CI, confidence interval; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; HR, hazard ratio; PEA, pulseless electrical activity; VT, ventricular tachycardia; VF, ventricular fibrillation; WLST, withdrawal of life-sustaining therapy.

discharge (alive) and death as competing risks. We also characterized the cumulative incidence of in-hospital death with and without prior GOC discussions using a multistate model. Both competing risk and multistate analyses were used to address different aspects of our study. The competing risk model estimated the incidence rate of documented GOC discussions, whereas the multistate model offered a more comprehensive understanding of patient transitions and outcomes after these discussions, enabling a fuller characterization of the patients' clinical journey.

Missing variables were imputed using multiple imputation using chained equations (MICE), and results of regression models on imputed data sets were combined using Rubin's rule. All analyses were performed in R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

During the study period, 264 patients were admitted to participating hospitals following OHCA, with baseline characteristics stratified by survivorship listed in Table 1. In the overall cohort, the median age of patients was 66 years (54-78), with 76.5% (n = 202) being male. Admissions were evenly split, with 50% (n = 132) in the coronary care unit and 50% in the medical-surgical intensive care unit. Patients were admitted for a median of 6 days (2-14), with a crude mortality rate of 62.1% (n = 164). Bystander CPR was initiated in 61.5% (n = 107) of cases. A shockable rhythm (ie, ventricular fibrillation or ventricular tachycardia) was documented as the initial rhythm in 80 (46.2%) patients. Median (Q1-Q3) documented EMS response time was 5 (3-7) minutes. It was estimated using the Fine-Gray subdistribution method that 60.6% (95% CI: 55.0%, 66.8%) of total patients died during the hospitalization by the end of week 6. Conversely, less than one-third (32.6%, 95% CI: 27.4%, 38.7%) of the patients were discharged alive by the end of week 6 (86 of 100 survivors).

Among the 164 patients who died, 67.1% (n = 110) of patients died following a decision to withdraw life-sustaining therapy, with 90% (n = 99) of these being a result of concern regarding neurologic prognosis directly because of OHCA-related anoxic brain injury. Other documented reasons for WLST in the remaining patients stemmed from medical complications and prior expressed wishes. Only 9.8% (n = 16) of patients were formally declared brain dead, with death confirmed at the moment of declaration. In patients from whom life-sustaining therapy was withdrawn, 50% (n = 55) occurred <72 hours from admission; Figure 1 outlines the trajectory of all patients admitted following OHCA.

WLST in OHCA

The time-varying associations of clinical factors at admission with the timing of WLST within 72 hours are quantified and summarized in Table 2. Nonlinear effects of continuous covariates (ie, age, EMS response time, and initial lactate) are further illustrated graphically in Figure 2. The results of cause-specific hazard regression showed that age had a significant nonlinear association with death following WLST within 72 hours post admission (Fig. 2 left panel, $P = 0.002$). Specially, the regression-adjusted age effect was nearly flat before 65 years and increased substantially after 65 years. Patient's age was the only clinical factor significantly associated with death

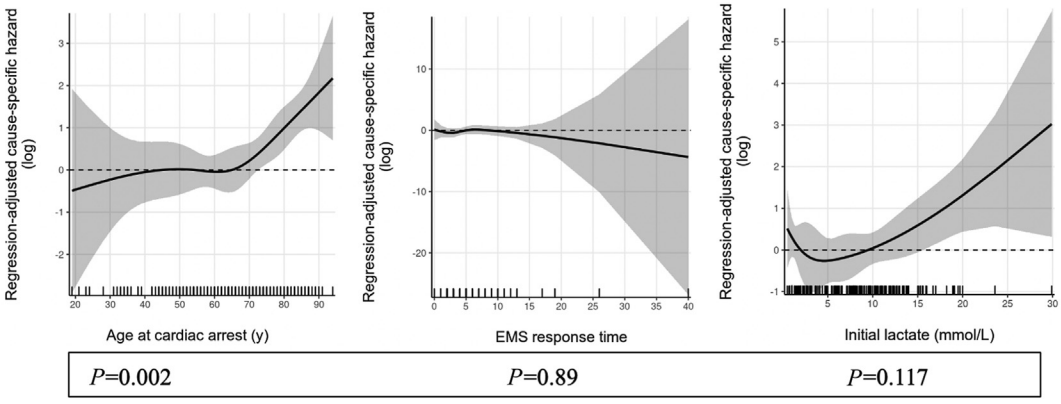

Figure 2. The nonlinear effects of continuous covariates (age, EMS response time, initial lactate) on WLST within 72 hours, estimated and summarized using natural cubic splines and shown graphically on a log hazard scale. EMS, emergency medical services; WLST, withdrawal of life-sustaining therapy.

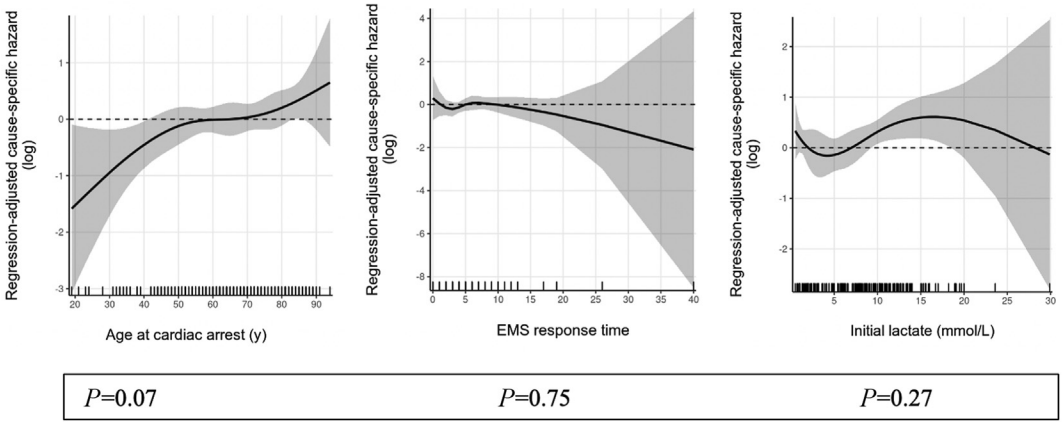

Figure 3. The nonlinear effects of continuous covariates on GOC discussion estimated and summarized using natural cubic splines. *EMS*, emergency medical services; *GOC*, goals of care.

following WLST within 72 hours of admission (Table 2). Supplemental Table S1 and Figure S1 summarize the associations of the prespecified clinical factors with death following WLST ≥72 hours post admission.

GOC discussions in OHCA

GOC discussions were documented in 56.4% (n = 149) of patients with a median age of 69 years (57-79) and 72.5% being males (n = 108). Of those with documented GOC discussions, 129 patients subsequently died and 20 were discharged alive. Using the Fine-Gray subdistribution method, it was estimated that a cumulative 31.8% (95% CI: 26.7%, 38.0%), 38.6% (95% CI: 33.2%, 45.0%), and 42% (95% CI: 36.5%, 48.4%) of the 264 patients had a documented GOC discussion within the first 24, 48, and 72 hours after admission, respectively (Supplemental Fig. S2). By the end of week 6, 56.1% (95% CI: 50.4%, 62.4%) of the patients had a GOC discussion before discharge or death. The results of cause-specific hazard regression suggest that initial recorded arrest rhythms of asystole and PEA were associated with documented GOC discussions ($P = 0.003$). Subsequent GOC were also more likely to be discussed during admission in patients with asystole as the initial arrest rhythm (HR = 2.540, 95% CI: 1.481, 4.357). Although age was not significantly associated with documented GOC discussions ($P = 0.07$), GOC discussions were increasingly more likely in older patients (Fig. 3). Age, sex, BMI, EMS response time, bystander CPR, and initial lactate were not significantly associated with documented GOC discussions (Table 3).

Association of documented GOC discussions with clinical outcomes

Expanding a competing risk model to a multistate model, it was estimated that, by the end of week 6 post admission, 47.3% (95% CI: 41.5%, 54.0%) and 13.3% (95% CI: 11.8%, 14.9%) of patients died with and without prior documented GOC discussions, respectively. Goals of care discussion documentation and their associated timing were associated with patient care trajectories as seen in Figure 4. On the one hand, GOC documentation within 72 hours was significantly associated with the mortality for all modes of deaths (death following WLST: HR = 15.609, 95% CI: 8.909, 27.349, $P < 0.001$; death on life-supporting therapy: HR = 6.751, 95% CI: 2.682, 16.991, $P < 0.001$; with CPR: HR = 5.278, 95% CI: 2.002, 13.916, $P < 0.001$; brain death: HR = 5.553, 95% CI: 2.010, 15.345, $P < 0.001$). On the other hand, GOC documentation after 72 hours was significantly associated with death following WLST only (HR = 21.068, 95% CI: 10.020, 44.297, $P < 0.001$).

Discussion

This retrospective cohort study examined the trajectory of patients following OHCA within a multicentred, tertiary academic hospital setting, focusing on nonsurvivors and the application and timing of WLST and GOC discussions. To our knowledge, this is the first study to explore WLST in an exclusively Canadian cohort and demonstrates previously undescribed practices with respect to the incidence of GOC documentation in this vulnerable patient population, in which these discussions could influence patterns of care and survival.

Our study demonstrated several key findings. Notably, we observed that among patients who underwent WLST, 90% of these decisions were attributed to a perceived poor neurologic prognosis, with 50% occurring within 72 hours of admission.

Table 3. The results of cause-specific hazard regression summarized for GOC discussion

Clinical factors	HR (95% CI)	*P* value
Age, y	Nonlinear (Fig. 3)	0.070
Female, vs male	1.440 (0.954, 2.175)	0.082
Calculated EMS response time, min	Nonlinear (Fig. 3)	0.75
Initial lactate, mmol/L	Nonlinear (Fig. 3)	0.27
BMI, vs normal		1.00
Obese	0.991 (0.591, 1.662)	
Overweight	0.969 (0.582, 1.614)	
Underweight	1.033 (0.395, 2.702)	
Bystander CPR administration, vs no CPR	0.742 (0.468, 1.176)	0.20
Initial arrest rhythm		0.003
Asystole	2.540 (1.481, 4.357)	
PEA	1.418 (0.825, 2.438)	
Female	1.405 (0.708, 2.788)	0.32

BMI, body mass index; CI, confidence interval; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; HR, hazard ratio; PEA, pulseless electrical activity; GOC, goals of care.

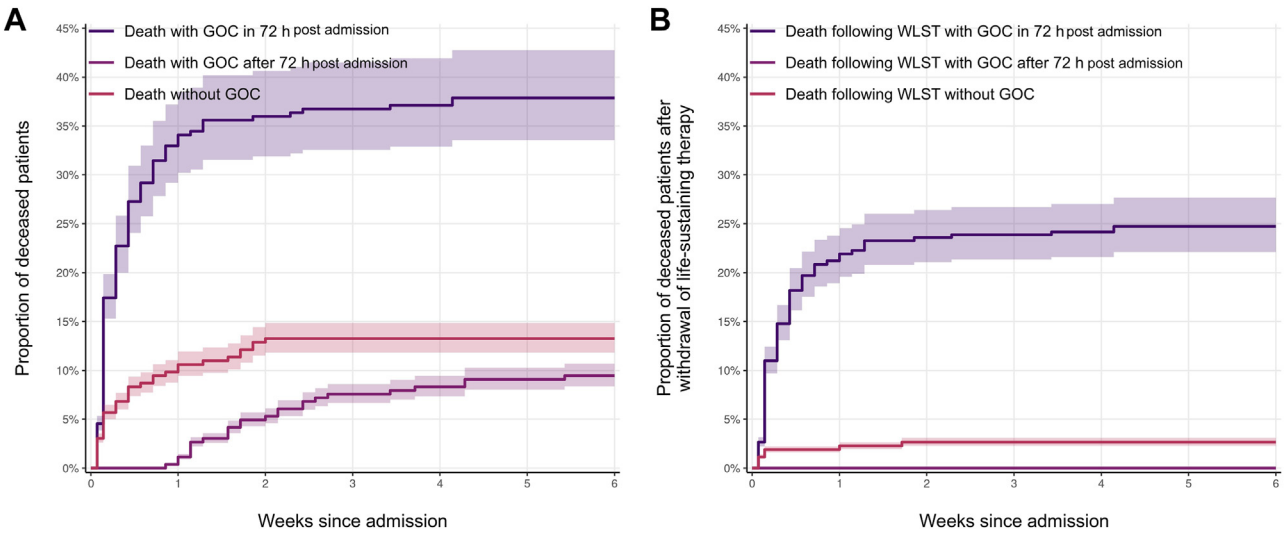

Figure 4. The cumulative proportion of deceased patients with post-arrest GOC within 72 hours, after 72 hours, and with no GOC with respect to time in (**A**) overall deceased patients and (**B**) patients following WLST. WLST, withdrawal of life-sustaining therapy; GOC, goals of care.

Increasing age made WLST within 72 hours more likely, with a risk significantly higher in a 75- vs 65-year-old patient (HR = 1.847, 95% CI 1.188, 2.871). Among nonsurvivors, formal declaration of brain death occurred in only 9.8% of cases, compared with 67.1% of patients receiving WLST. These findings, although consistent with previous literature, suggest a possible deviation from established guidelines that recommend minimum observation periods before definitive prognostic conclusions. Given that 60% of patients who died after OHCA were also on targeted temperature management (TTM), this may underestimate the incidence of guideline-nonconcordant WLST, as guidelines recommend waiting an additional 72 hours after TTM completion. When GOC conversations are documented, the likelihood of WLST is significantly increased across all time periods, which may reflect the increased propensity to document during critical patient care decisions.

These insights may indicate physician belief in poor prognosis for many patients, leading to early WLST, with or without documented GOC discussions. In some patients, GOC discussions may be a tool for education and informed shared decision making for patient care, leading to WLST. What is most likely is that there is a complex interplay of both situations, taking into consideration patient, physician and substitute decision maker dynamics. While the 72-hour cut-off has been shown to minimize false positive rates in terms of clinical tests for poor neurologic outcomes, this should be contextualized in terms of each patients' unique presentation, neurologic assessment, comorbidities, and patient preferences for quality of life.

This retrospective cohort study, while revealing important insights, has inherent limitations. The retrospective design restricts our ability to establish causal relationships and may involve unintended biases in data collection and interpretation. Additionally, the study's findings are based on historical data, which may not fully capture current practices or emerging trends in WLST decision making. However, contemporary guidelines used the same 72-hour guideline that remains today, and in many cases requiring longer observation periods because of TTM, allowing us to infer current practices.[19,20] This study captures a large, urban, multicentred, tertiary academic Canadian cohort that reflects OHCA practices before the COVID-19 pandemic whereby these data may have been influenced by extenuating factors. These sites were all within the same city and may reflect different practices when compared to similar institutions in other Canadian cities or smaller community centers. Because GOC discussions were inferred from their documentation, this may not capture all possible discussions and might reflect the lack of documentation in many critically ill patients rather than the absence of a discussion.

There is heterogeneity of practice in the care of patients post-OHCA, and initiation and documentations of GOC discussions may provide an opportunity for education and shared decision making. Future research may benefit from understanding what supplemental data different clinicians use when making decisions around WLST, and how they are weighted, in the absence of formal neuroprognostication. Although clinical guidelines exist for neuroprognistication post-OHCA, further research is needed to identify the needs of physicians, patients, as well as their families in terms of making complex decisions around WLST.

Ethics Statement

The research reported in this paper adhered to all relevent ethical guidelines recommended by each hospital Research Ethics Board.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective case report using de-identified data; therefore, the Research Ethics Board did not require consent from the patient.

Funding Sources

This study was supported by a Resident Research Grant from Mount Sinai Hospital, Toronto, Ontario, Canada.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2024.11.013