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Clinical paper

Early advanced life support attendance is associated with improved survival and neurologic outcomes after non-traumatic out-of-hospital cardiac arrest in a tiered prehospital response system

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Abstract

Objective: Data demonstrating benefit of advanced life support (ALS) practitioners for out-of-hospital cardiac arrest (OHCA) is conflicting. In our tiered emergency medical services (EMS) system, we sought to determine if the ALS response interval was associated with patient outcomes.

Methods: We performed a secondary analysis of consecutive adult OHCAs (2006–2016) in British Columbia. Primary and secondary outcomes were survival and favorable neurological outcomes (mRS $\leq$ 3) at hospital discharge. Logistic regression estimated the association of ALS response interval (911 call-to-ALS arrival, continuous and categorical analyses) and outcomes, adjusting for first EMS response interval, and other clinical characteristics. We calculated the optimal time threshold to differentiate "early" vs "late" ALS response intervals for a binary comparison.

Results: Of 12,722 included cases, 12% survived to discharge. Median response interval was 6.4 min (IQR 5.2–8.3) for the first EMS unit and 11.8 min (IQR 8.7–16.5) for ALS. ALS response interval (per minute) was associated with decreased survival (adjusted OR 0.98, 95% CI 0.96–0.99) and favourable neurological outcome (0.98, 95% CI 0.97–0.99). ALS response $\leq$10 min (the optimal threshold) was associated with improved survival (adjusted OR 1.46; 95% CI 1.27–1.68) and favourable neurological outcomes (adjusted OR 1.41; 95% CI 1.18–1.68).

Conclusion: In our tiered EMS system, earlier ALS arrival was associated with improved survival and favorable neurological outcomes. ALS attendance within 10 min of the 9-1-1 call in tiered systems of prehospital care may improve patient outcomes and serve as a quality metric.

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Introduction

Out-of-hospital cardiac arrest (OHCA) management includes basic life support (BLS) maneuvers (e.g. chest compressions, defibrillation, and bag-mask ventilation) and advanced life support (ALS) treatments (e.g. intravenous pharmacotherapies and advanced airway management). EMS systems commonly deploy ALS-trained personnel to treat OHCAs, predicated on the assumption that the addition of ALS interventions is superior to BLS measures alone. There are no randomized data to experimentally evaluate the benefit of prehospital ALS management, and observational data is conflicting.[1–6]

We postulated that if prehospital ALS care imparts a clinical benefit, then a delay should be associated with poorer outcomes. Likewise, if prehospital ALS care imparts benefit to OHCA subjects, the optimal timing of ALS arrival is unknown. On one hand, the initial care provided by BLS- and ALS-trained providers is the same — chest compressions, defibrillation (as indicated), and basic airway maneuvers. Thus, benefit of ALS care may only be observed after the initial basic resuscitation has failed to yield return of circulation (ROSC). Moreover, ALS therapies may distract from the provision of high quality BLS therapies. Conversely, waiting too long to institute ALS therapies may be offer little benefit to a patient after prolonged refractory arrest.[7]

It is currently unclear to what extent ALS resources should be available in the prehospital setting, and if there should be goal metrics for ALS response intervals. In this study, we investigated the time-dependent effects of ALS deployment on clinical outcomes after OHCA. We sought to determine if ALS response interval was associated with outcomes, and if there was a time interval during resuscitation in which ALS would impart the most benefit.

Methods

Study setting

British Columbia (BC) was a member of the Resuscitation Outcomes Consortium (ROC), a 10-site North American trial network that maintained a comprehensive registry of non-traumatic OHCA cases, from 2005 to 2016.[8] The ROC catchment area in BC includes the four metropolitan regions (Greater Victoria and Nanaimo, Greater Vancouver and the north shore, the Fraser Valley, and Kelowna/Kamloops), which contained 3.3 million citizens as of the 2011 census, approximately 75% of the province's population.[9,10] The institutional ethical review boards of Providence Health Care and the University of British Columbia approved this study.

EMS organization and medical care

The province of British Columbia employs a single EMS with central leadership and standardized protocols. The EMS is a coordinated effort between the provincial BC Emergency Health Services (BCEHS) and municipal fire departments (FD), trigged by a provincial 9-1-1 service. Prehospital response for OHCAs is a tiered strategy with the following EMS units simultaneously dispatched, typically arriving in this order: a BLS-trained FD unit, a BLS-trained BCEHS unit, and an ALS-trained BCEHS unit. BLS providers perform chest compressions, bag-valve mask ventilation, and apply AEDs. ALS providers perform intubation, intravenous and intraosseus access, and deliver intravenous advanced cardiovascular life support (ACLS) medications.[11] Provincial EMS protocols are developed by BCEHS and are publically available.[12] In the BC ROC geographical catchment approximately 17% of BCEHS units are ALS-trained.

Data collection

The BC ROC research unit prospectively identified all EMS-treated OHCAs, defined as those receiving chest compressions from a professional rescuer, or any defibrillation from a professional or lay rescuer. Prehospital data collection included treating providers, subject characteristics, treatments administered, and outcomes, as well as the including timing of all events. Hospital charts were then manually reviewed to abstract discharge outcomes and additional data as necessary for specific clinical trials. During the study period there were clinical trials performed which enrolled consecutive non-traumatic OHCA, the PRIMED study and the CCC study.[13–15] Data on neurologic outcomes at discharge were only collected for patients enrolled in a clinical trial.

Selection of participants and outcome measures

We included EMS-treated adult subjects (age $\geq$ 18) from the BC ROC registry between 2005 and 2016. We excluded cases with EMS-witnessed collapse, a "do not resuscitate" order, and those not treated by ALS. The primary outcome was survival at hospital discharge; the secondary outcome was favourable neurological outcome, defined as modified Rankin scale (mRS) $\leq$ 3.[16]

Data analysis

We used Microsoft Excel 2008 (Microsoft Corp, Redmond, WA,) and STATA version 13.1 (STATA Corp, College Station, TX) for data analysis. In our primary analysis, logistic regression analysis estimated the association between ALS response interval (elapsed interval from 9-1-1 call to ALS on-scene arrival; continuous variable) and clinical outcomes. We adjusted for known Utstein covariates[8,16] including age, sex, initial EMS-recorded cardiac rhythm (shockable, non-shockable, and unclassified), bystander and/or EMS witnessed collapse, bystander CPR, location of the event (public or non-public), and first EMS arrival response interval (elapsed time from 9-1-1 call until first EMS arrival, whether FD-BLS, BCEHS-BLS, or BCEHS-ALS units), as well as year of treatment (categorized as 2005–2008, 2009–2012, and 2013–2016). The variance inflation factor (VIF) tested for multicollinearity, and the Hosmer-Lemeshow goodness-of-fit test determined the suitability of model fit for the primary outcome. In addition, we calculated area under the receiver operating characteristic (ROC) curve to assess discrimination of this model for the primary outcome.

We employed multiple imputation to address missing data, maximize statistical power, and minimize bias from excluding those subjects with missing data,[17] developed for STATA, version 13.1.[18] Missing data was considered to occur at random. Imputation models included ALS response interval, model covariates, and outcomes (ROSC, survival, and neurological status at hospital discharge). Fifty datasets with missing data replaced by imputed variables were created and analyzed separately. Resulting estimates and standard errors were combined by Rubin's rule, accounting for within and between data set variance.[18] We performed the primary analysis with multiple imputation, however performed additional sensitivity analyses limited to those with complete cases capture.

We performed several secondary analyses using similar methods as the primary analysis. We classified ALS response interval as a categorical variable (quintiles and deciles) to explore whether the association of ALS response interval differed within incremental segments of the resuscitation. We also examined subject subgroups stratified by initial rhythm, (shockable vs. non-shockable) and witnessed vs. unwitnessed collapse.

To visualize the association of ALS response interval and outcomes, we plotted predicted outcomes as a function of ALS response interval (minutes), modeling with restricted cubic splines with four knots in the same logistic regression.[19] The spine model examining neurological outcomes included only subjects with complete outcome data.

Finally, we tested thresholds of ALS response using previously described methods,[20,21] in order to determine the optimal cut-point to differentiate the impact of "early" and "late" ALS response. First, we computed the area under the ROC curve derived from the unadjusted logistic regression model to assess the association between the probability of survival at discharge and ALS response interval. We then calculated the shortest 0/1 distance and the greatest Youden index. The 0/1 distance is measured between the curve and the (0,1) point on the graph. The Youden index is the point on the ROC curve maximizing sensitivity and specificity (calculated as the sum of sensitivity and specificity-1). Second, we performed a series of multivariable logistic regression models, assessing the association between survival and early (vs late) ALS response (dichotomized at each possible integer value). From each model we calculated the Z-statistic (the beta estimate divided by the standard error of the beta). To identify the optimal discriminating threshold, we graphed the 0/1 distance, the Youden index, and Z-statistics for all cutoffs between 0 and 30 min of ALS arrival time in the total cohort. We used the ROC models to determine the approximate threshold, and the Z-statistic method to determine the exact value. Then, using the optimal threshold value, we assessed the association of "early" vs "late" ALS response interval and outcomes, using the same multivariable logistic regression methods as the primary analysis, in the multiply imputed cohort as those with complete case capture.

Results

Characteristics of study subjects

Of 26,562 non-traumatic OHCAs identified during the study period, 12,722 ALS-treated cases were included in the final cohort (Fig. 1, Appendix A in Supplementary material). Trial-enrolled patients were similar to the full cohort (Appendix B in Supplementary material).

Main results

Overall patient characteristics are shown in Table 1. The median response interval was 6.4 min (IQR 5.2–8.3) for the first EMS unit and 11.8 min (IQR 8.7–16.5) for ALS, who arrived first in 11% of cases. The median number of BLS-trained personnel on scene prior to ALS arrival was 5 (IQR 4–6). A total of 6085 (48%) achieved ROSC and 1471 (12%) survived to hospital discharge. Of the 891 survivors with neurological outcome data, 779 (87%) had favorable neurological outcomes.

Table 2 shows adjusted ORs for survival and neurological outcome based on ALS response interval. No variables were co-linear and the models had acceptable fit (Appendix C in Supplementary material). For each one-minute increase in ALS response interval, the adjusted odds of survival (adjusted OR 0.98 per minute, 95% CI 0.96–0.99) and favorable neurological outcome (adjusted OR 0.98 per minute, 95% CI 0.97–0.99) decreased. Area under ROC was 0.85 (95% CI 0.84–0.87). The analyses with complete case data yielded similar results.

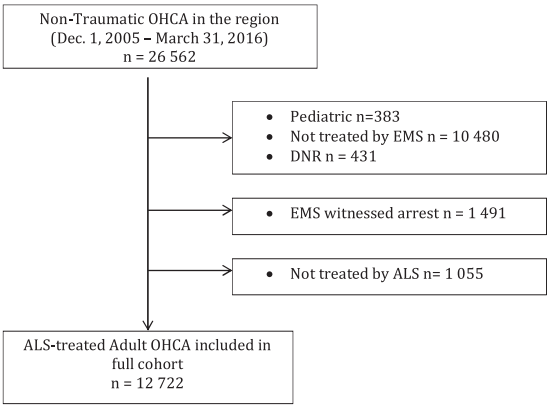

Fig. 1 – Study flow.

Secondary results

Patient characteristics, divided into quintiles of ALS response interval, are illustrated in Table 1. Table 3 demonstrates the stepwise decline in the odds of survival and favorable neurological outcomes with longer ALS response intervals, compared to the shortest ALS time response category. The logistic regression models had acceptable fit (area under ROC was 0.85, 95% CI 0.84–0.87).

Logistic regression models of subgroups dichotomized by initial cardiac rhythm and witnessed status are also contained in Table 3 and Appendix D in Supplementary material. The models testing ALS response interval in deciles (Appendix E in Supplementary material) demonstrated similar results.

Spline curves demonstrate the estimated decrease in survival at hospital discharge and favorable neurological outcomes as a function of ALS response interval (Fig. 2).

Based on two ROC-curve methods, the optimal threshold to differentiate the impact of "early" and "late" ALS response was between 10 and 12 min (Appendix F in Supplementary material). Within this range, the maximum Z-statistics in the adjusted logistic regression model was observed when ALS time was dichotomized at $\leq$ or $>$10 min (Table 4). Using the threshold of $\leq$10 min to dichotomize ALS response interval, we found that early (vs late) ALS response interval was associated with survival (adjusted OR 1.46; 95% CI 1.28–1.68) and neurological outcomes (adjusted OR 1.36; 95% CI 1.17–1.59) at hospital discharge (in the multiply imputed cohort). When restricting this analysis to those with complete data in the total cohort, early ALS response interval was associated with survival (adjusted OR 1.46; 95% CI 1.27–1.68) and neurological outcomes (adjusted OR 1.41; 95% CI 1.18–1.68).

Discussion

We examined a cohort of OHCA subjects treated within a large single provincial EMS system with tiered deployment. After adjustment,

Table 1 – Patient characteristics, full cohort and divided by als response interval (quintiles).

	Total cohort		ALS response interval, categorical (quintiles)											
	(n = 12,722)		0 – < 8.1 min (n = 2565)		8.1 – <10.6 min (n = 2562)		10.6 – <13.3 min (n = 2491)		13.3 – <18.1 min (n = 2548)		≥18.1 min (n = 2532)		No ALS time (n = 24)	
Variable	n or Median	Missing (%)	n or Median	Missing (%)	n or Median	Missing (%)	n or Median	Missing (%)	n or Median	Missing (%)	n or Median	Missing (%)	n or Median	Missing (%)
Patient charactors														
Age (IQR), y	67 (54–79)	167 (1.3)	66 (53–79)	34 (1.3)	67 (54–79)	33 (1.3)	69 (55–81)	29 (1.2)	67 (55–79)	33 (1.3)	67 (55–79)	26 (1.0)	68 (49–79)	12 (50.0)
Male sex (%)	8729 (68.9)	53 (0.4)	1769 (69.1)	5 (0.2)	1769 (69.4)	12 (0.5)	1702 (68.6)	10 (0.4)	1747 (68.7)	6 (0.2)	1734 (68.7)	8 (0.3)	8 (66.7)	12 (50.0)
Initial rhythm (%)		345 (2.7)		79 (3.1)		71 (2.8)		63 (2.5)		71 (2.8)		50 (2.0)		11 (45.8)
Shockable VF/pVT (%)	3,199 (25.9)		706 (28.4)		618 (24.8)		636 (26.2)		626 (25.3)		611 (24.6)		2 (15.4)	
Non-shockable														
–Asystole (%)	1967 (15.9)		426 (17.1)		385 (15.5)		369 (15.2)		371 (15.0)		412 (16.6)		4 (30.8)	
–PEA (%)	5203 (42.0)		1123 (45.2)		1046 (42.0)		967 (39.8)		1030 (41.6)		1031 (41.5)		6 (46.2)	
–AED no-shock (%)	1912 (15.5)		210 (8.5)		422 (16.9)		442 (18.2)		432 (17.4)		405 (16.3)		1 (7.7)	
–Unclassifiable (%)	96 (0.8)		21 (0.8)		20 (0.8)		14 (0.6)		18 (0.7)		23 (0.9)		–	
Bystander witnessed (%)	5671 (44.6)	0	1123 (43.8)	0	1084 (42.3)	0	1122 (45.0)	–	1150 (45.1)	0	1186 (46.8)	0	6 (25.0)	0
Location (%)		22 (0.2)		2 (0.1)		2 (0.1)		4 (0.2)		0		2 (0.1)		12 (50.0)
Public location (%)	2464 (19.4)		544 (21.2)		473 (18.5)		438 (17.6)		521 (20.5)		485 (19.2)		3 (25.0)	
Non-public location (%)	10,236 (80.6)		2019 (78.8)		2087 (81.5)		2049 (82.4)		2027 (79.6)		2045 (80.8)		9 (75.0)	
Bystander CPR (%)	6311 (49.6)	0	1260 (49.1)	0	1255 (49.0)	0	1239 (49.7)	–	1321 (51.8)	0	1230 (48.6)	0	6 (25.0)	0
Time to first EMS arrival (IQR), min	6.4 (5.2–8.3)	199 (1.6)	5.3 (4.3–6.3)	30 (1.1)	6.3 (5.1–7.8)	33 (1.3)	6.6 (5.3–8.3)	34 (1.4)	7.0 (5.7–8.8)	35 (1.4)	8.2 (6.3–11.4)	55 (2.2)	7.5 (4.5–10.2)	12 (50.0)
ALS arrival time (IQR), min	11.8 (8.7–16.5)	24 (0.2)												
Year of treatment		0		0		0		0		0		0		0
2005–2008 (%)	3,546 (27.9)		809 (31.5)		715 (27.9)		671 (26.9)		646 (25.4)		700 (27.7)		5 (20.8)	
2009–2012 (%)	4120 (32.4)		765 (29.8)		845 (33.0)		779 (31.3)		900 (35.3)		828 (32.7)		3 (12.5)	
2013–2016 (%)	5056 (39.8)		991 (38.6)		1002 (39.1)		1041 (41.8)		1002 (39.3)		1004 (39.7)		16 (66.7)	
ALS arrival on scene first (%)	1390 (11.0)	63 (0.5)	939 (36.7)	5 (1.9)	273 (10.7)	4 (0.2)	92 (3.7)	10 (0.4)	51 (2.0)	10 (0.4)	33 (1.3)	33 (1.3)	2 (8.7)	1 (4.2)
Number of personnel before ALS arrival (IQR), n	5 (4–6)	1113 (8.7)	2 (0–2)	111 (4.3)	4 (3–6)	161 (6.3)	6 (4–6)	163 (6.5)	6 (4–6)	232 (9.1)	6 (4 –6)	441 (17.4)	4 (2–6)	5 (20.8)
ALS treatments														
Advanced airway placement (%)	10,813 (85.0)	0	2267 (88.4)		2194 (85.6)		2129 (85.5)		2145 (84.2)		2073 (81.9)		5 (20.8)	
Supraglottic airway (%)	965 (7.6)	0	112 (4.4)		108 (4.2)		124 (5.0)		214 (8.4)		404 (16.0)		3 (12.5)	
Endotracheal airway (%)	10,309 (81.0)	0	2221 (86.6)		2133 (83.3)		2066 (83.0)		2045 (80.3)		1841 (72.7)		3 (12.5)	
Epinephrine (%)	10,103 (79.4)	0	2115 (82.5)		2080 (81.2)		2007 (80.6)		1999 (78.5)		1900 (75.0)		2 (8.3)	
Amiodarone (%)	1118 (8.8)	0	239 (9.3)		233 (9.1)		218 (8.8)		245 (9.6)		182 (7.2)		1 (4.2)	
Outcomes														
ROSC (%)	6085 (47.8)	2 (<0.1)	1363 (53.1)	0	1216 (47.5)	0	1202 (48.3)	–	1197 (47.0)	0	1103 (43.6)	0	4 (18.2)	2 (8.3)
Survival at hospital discharge (%)	1471 (11.7)	147 (1.2)	420 (16.6)	40 (1.6)	306 (12.1)	30 (1.2)	259 (10.5)	26 (1.0)	276 (10.9)	24 (0.9)	207 (8.3)	19 (0.8)	3 (18.9)	8 (33.3)
Survivors with favorable neuro outcomes (%)[a]	779 (6.5)	726 (5.7)	208 (8.8)	209 (8.1)	181 (7.5)	136 (5.3)	140 (5.9)	128 (5.1)	151 (6.2)	127 (5.0)	97 (4.0)	117 (4.6)	2 (13.3)	9 (37.5)

*ALS, advanced life support; VF, ventricular fibrillation; pVT, pulseless tachycardia; PEA, pulseless electrical activity; EMS, emergency medical system; ROSC, return of spontaneous circulation; neuro, neurological.

[a] Note: all missing neurological outcomes were in those who survived to hospital discharge.

Table 2 – Logistic regression analysis (main analysis, als response interval continuous).

	Survival to discharge		Favourable neurological outcome	
	Multiply imputed cohort n = 12,722 Adjusted OR (95% CI)	Complete data case n = 12,024 Adjusted OR (95% CI)	Multiply imputed cohort n = 12,722 Adjusted OR (95% CI)	Complete data case n = 11,533 Adjusted OR (95% CI)
ALS interval (per min)	0.98 (0.96–0.99)	0.97 (0.96–0.98)	0.98 (0.97–0.99)	0.98 (0.96–0.99)
Age	0.97 (0.97–0.98)	0.97 (0.97–0.98)	0.97 (0.96–0.97)	0.97 (0.96–0.97)
Sex (male vs female)	0.89 (0.76–1.03)	0.91 (0.78–1.07)	0.91 (0.76–1.07)	0.96 (0.78–1.18)
Shockable rhythm	8.58 (7.39–9.56)	8.94 (7.70–10.39)	8.92 (7.53–10.57)	8.60 (7.06–10.47)
Witnessed arrest	2.63 (2.27–3.05)	2.61 (2.24–3.05)	2.80 (2.37–3.31)	2.92 (1.48–2.12)
Location (public vs private)	2.02 (1.76–2.31)	1.79 (1.55–2.07)	1.95 (1.68–2.27)	1.77 (1.48–2.12)
Bystander CPR	1.09 (0.96–1.25)	1.09 (0.95–1.25)	1.20 (1.03–1.39)	1.27 (1.06–1.52)
Response interval to first EMS arrival (per min)	0.94 (0.91–0.96)	0.92 (0.90–0.95)	0.93 (0.90–0.96)	0.92 (0.89–0.96)
Year 2005–2008	Reference	Reference	Reference	Reference
2009–2012	1.53 (1.29–1.80)	1.49 (1.25–1.77)	1.53 (1.25–1.86)	3.38 (2.60–4.38)
2013–2016	1.85 (1.57–2.17)	1.67 (1.41–1.97)	2.09 (1.71–2.55)	3.66 (2.83–4.73)

Table 3 – Logistic regression analysis with categorial als response interval (quintiles), full cohort and subgroups.

		Total	Witnessed vs non-witnessed		Shockable or non-shockable initial rhythm	
		n = 12,722	Witnessed n = 5671	Non-witnessed n = 7051	Shockable n = 3295	Non-shockable n = 9396
Outcome	Elapsed Time to ALS arrival	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Survival	<8.1 min	Reference	Reference	Reference	Reference	Reference
	8.1 min – < 10.6 min	0.75 (0.63–0.91)	0.71 (0.56–0.89)	0.88 (0.63–1.23)	0.72 (0.57–0.92)	0.80 (0.58–1.10)
	10.6 min – < 13.3 min	0.61 (0.50–0.74)	0.60 (0.48–0.76)	0.61 (0.42–0.88)	0.53 (0.41–0.67)	0.76 (0.54–1.05)
	13.3 min – < 18.1 min	0.63 (0.52–0.77)	0.63 (0.50–0.80)	0.63 (0.44–0.90)	0.60 (0.47–0.77)	0.67 (0.47–0.95)
	≥ 18.1 min	0.52 (0.41–0.64)	0.50 (0.38–0.64)	0.59 (0.39–0.89)	0.49 (0.38–0.65)	0.54 (0.37–0.80)
Favorable neurological outcome	<8.1 min	Reference	Reference	Reference	Reference	Reference
	8.1 min – < 10.6 min	0.84 (0.68–1.04)	0.81 (0.63–1.03)	0.96 (0.65–1.42)	0.80 (0.62–1.03)	0.93 (0.64–1.35)
	10.6 min – < 13.3 min	0.67 (0.54–0.88)	0.65 (0.50–0.83)	0.75 (0.49–1.14)	0.60 (0.46–0.78)	0.85 (0.57–1.26)
	13.3 min – < 18.1 min	0.70 (0.56–0.87)	0.70 (0.55–0.91)	0.69 (0.45–1.06)	0.66 (0.51–0.87)	0.78 (0.52–1.17)
	≥18.1 min	0.61 (0.47–0.77)	0.58 (0.44–0.76)	0.73 (0.46–1.16)	0.56 (0.42–0.75)	0.71 (0.46–1.10)

including response interval to first EMS contact, we found that earlier attendance of ALS providers was associated with improved survival and favorable neurological outcomes. ALS response interval initially demonstrated a step-wise decline in the odds of survival with increasing intervals, however this decline stabilized at approximately 10 min. Ten minutes was the optimal threshold to discriminate "early" vs "late" ALS response interval, and found that early ALS response was associated with survival and neurological outcomes. Collectively, these data suggest that the greatest benefit of ALS involvement may be within the first 10 min of the resuscitation. These data may assist other tiered prehospital systems in creating ALS response time targets and in resource planning for the number and proportion of ALS units.

We originally hypothesized that there would be minimal association between ALS response interval and outcomes within the early stages of the resuscitation, since early critical interventions – high quality CPR and defibrillation – would be aptly performed by BLS providers. However, our data demonstrate an initial sharp decline in the probability of positive outcomes with increasing delays to ALS arrival, stabilizing around the 10-min mark. Similarly, we found that 10 min was the best threshold to discriminate the association of early vs late ALS arrival. These data suggest that the benefit of ALS beyond 10 min may be substantially reduced.

We examined the association of ALS response interval, rather than comparing treatment with or without ALS involvement — a comparison that poses significant challenges when using observational data. Within tiered EMS systems, OHCAs treated with or without ALS may represent systematically different populations; for example, ALS may be preferentially triaged to OHCAs with certain characteristics,[2] thus confounding comparisons. Alternatively, access to ALS may vary by geographical locations, where patient characteristics and hospital-based medical care may also differ. BLS-only groups may include a higher proportion of patients who achieved rapid ROSC with defibrillation, and thus ALS units were re-directed to other calls. Among those excluded from our analysis due to BLS-only care (Appendix B in Supplementary material) there was a shorter elapsed interval until ROSC, suggesting that ALS units may have been re-directed in those who responded rapidly to BLS-performed defibrillation. Another analytical strategy is comparing different EMS exclusively using BLS- or ALS-trained practitioners, however this may be confounded by other site-specific characteristics. Some studies have examined

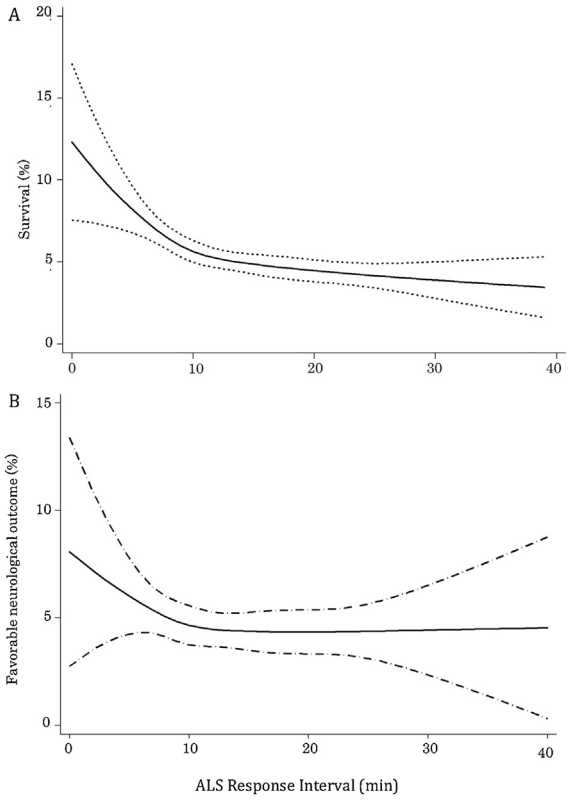

Fig. 2 – Spline curves for the outcomes of survival (A) and favorable neurological outcomes (B) at hospital discharge (with 95% confidence intervals), as a function of als response interval.

data from a large number of EMSs, comparing subjects treated with BLS-only or ALS care;[22] while external validity may be strengthened, internal validity may be compromised from system differences and may obscure the true benefit of ALS care in individual systems. To avoid these potential biases we examined an ALS-treated cohort and found that the likelihood of survival decreased with each additional minute of time to ALS arrival. Although we did not a compare BLS-only and ALS care, the dose-response relationship is suggestive of ALS benefit.

We did not seek to examine individual ALS maneuvers but rather the impact of ALS providers, who in our system are selectively triaged to critical cases. There are two ways in which ALS providers may impact resuscitations, the first being administering advanced treatments such as intravenous medications and intubation.[11] However, whereas BLS therapies have demonstrated improved outcomes,[23,24] advanced treatments lack robust evidence supporting their use.[25,26] The recent ROC Pragmatic Airway trial found worse outcomes among those randomized to endotracheal intubation.[27] The PARAMEDIC 2 trial[28] and ALPS Trial[25], investigating the benefits of epinephrine and amiodarone, respectively, both demonstrated no differences in neurological outcomes at hospital discharge. However, as patients were enrolled in these studies at approximately 20 min from the 9-1-1 call, the impact of these interventions prior to 10 min is unclear.

Secondly, an experienced ALS provider may confer benefit as an experienced code leader, a value beyond the sum of the individual treatments administered. Through training and experience, ALS paramedics may develop critical skills in rapid patient assessment, treatment decisions, and team-based leadership.[29] This yield may be variable depending on the system, perhaps with higher benefit in tiered systems with a low proportion ALS-trained units selectively triaged to the most critically ill subjects, and less benefit in regions with ALS-trained paramedics on all ambulances. An experienced paramedic may also improve post-arrest prehospital care. Within our tiered prehospital configuration only 1/6 of BCEHS units are ALS-trained. These units are preferentially dispatched to cardiac arrest cases, concentrating resuscitation experience, and thus are effectively specialized cardiac arrest response units. For this reason, the results of our analysis may not be applicable to systems with alternate configurations. Importantly, it is possible that non-ALS personnel who receive dedicated cardiac arrest training and are selectively triaged to OHCA events may confer the same benefit seen in our study. Finally, although our data demonstrates improved outcomes with earlier ALS arrival, it is possible that in adding more ALS members to a region (in order to decrease response times) there will be a detrimental effect from decreased experience in each paramedic. Further analyses are required explore the ideal configuration of prehospital providers with respect to training, response times, and experience.

Studies describing prehospital ALS management demonstrate conflicting results.[1–3] Sanghavi compared 31,292 ALS-treated subjects with 1643 BLS-treated subjects and the latter had higher survival, however was limited by an unconventional analysis and biases listed above.[2] Kurz and colleagues analyzed 35,065 OHCA, comparing groups of BLS-only, early ALS, and late ALS. They reported that ALS care was positively associated with survival to discharge, but only when provided within 6 min of first EMS arrival. [22] Our 10-min results are congruent with these findings when accounting for first EMS response time. The best evidence comes from the OPALS study, which compared outcomes before and after the incorporation of ALS paramedics into the EMS.[3] They reported no change in outcomes, however OHCA management has substantially changed since. Further, it is possible that practitioners in the new ALS system had limited clinical experience. More recently Bakalos and colleagues published a meta-analysis examining ALS vs BLS prehospital care, concluding that ALS care was associated with improved outcomes,[1] with the caveat that constituent studies had heterogeneity of study design and EMS arrangements.

Table 4 – Optimal threshold time for ALS arrival based on highest Z-statistics in the logistic regression in full cohort.

Threshold time for ALS arrival	Adjusted OR for survival (95% CI)	Z-statistics
≤8 min versus > 8 min	1.50 (1.28–1.75)	4.98
≤9 min versus > 9 min	1.43 (1.24–1.66)	4.85
≤10 min versus > 10 min	1.46 (1.27–1.68)	5.33
≤11 min versus > 11 min	1.41 (1.23–1.62)	4.91
≤12 min versus > 12 min	1.39 (1.21–1.59)	4.60

Limitations

This study, although using high quality prospectively collected data, was an observational analysis and is limited to conclusions of association. Our study subjects were identified from the metropolitan regions of one Canadian province with a single tiered paramedic service; patient characteristics and medical management in different settings may limit external validity. However this single large EMS evaluation strengthens internal validity. It is possible that unmeasured confounders, such as patient comorbidities or socioeconomic factors, may have influenced outcomes. Our results indicate that time to first EMS response interval was associated with ALS response interval; cases with longer response times may be those further from urban environments and post-arrest care (however may also represent cases in poorly accessible urban locations such as locked buildings or high-rises). There may also be differences in post-arrest care in regions that had longer ALS intervals. We did not restrict our analysis to subjects who remained in refractory arrest until the time of ALS arrival and some patients may have had ROSC preceding ALS arrival. However, excluding these would have obscured the real-world relationship between ALS arrival and outcomes and would negate the potential benefit of ALS-trained paramedics in post-arrest care. We had neurological outcome data for just over half of survivors, which widened confidence intervals around our point estimates. It is possible that the association of improved outcomes with ALS arrival was simply a benefit of an increased number of providers of any training-level; however this is unlikely given the small increase of two ALS providers added to a group of on-scene BLS providers.

Conclusion

In our tiered EMS system, earlier ALS arrival was associated with improved survival and favorable neurological outcomes. ALS attendance within 10 min of the 9-1-1 call may improve patient outcomes and may serve as a quality metric in tiered systems of prehospital care.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.12.003.

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