Effectiveness of Emergency Medical Services for Victims of Out-of-Hospital Cardiac Arrest: A Metaanalysis

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Study objective: To determine the relative effectiveness of differences in response time interval, proportion of bystander CPR, and type and tier of emergency medical services (EMS) system on survival after out of hospital cardiac arrest.

Methods: We performed a comprehensive literature search, excluding EMS systems other than those of interest (systems of interest were those comprising one tier with providers of basic life support [BLS] or advanced life support [ALS] and those comprising two tiers with providers of BLS or BLS-defibrillation followed by ALS), patient population of fewer than 100 cardiac arrests, studies in which we could not determine the total number of arrests of presumed cardiac origin, and studies lacking data on survival to hospital discharge. Metaanalysis using generalized linear model with dispersion estimation for random effects was then performed.

Results: Increased survival to hospital discharge was significantly associated with tier (P<.01), response time interval (P<.01), and bystander CPR (P=.04). A significant interaction was detected between response time interval and bystander CPR (P=.02). For the studies analyzed, survival was 5.2% in a one-tier EMS system or 10.5% in a two-tier EMS system. A 1-minute decrease in mean response time interval was associated with absolute increases in survival rates of .4% and .7% in a one-tier and two-tier EMS systems, respectively.

Conclusion: Increased survival to hospital discharge may be associated with decreased response time interval and with the use of a two-tier EMS system as opposed to a one-tier system. The data available for this analysis were suboptimal. Policymakers need more methodologically rigorous research to have more reliable and valid estimates of the effectiveness of different EMS systems.

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Heart disease is the most common cause of death in the United States.[1] Such deaths are often due to cardiac arrest, the sudden cessation of cardiac mechanical activity manifested by the absence of a detectable pulse, unresponsiveness, and lack of breathing.[2] Emergency medical services (EMS) systems have evolved into multifaceted advanced cardiac life support systems involving CPR, defibrillation, artificial ventilation, intubation, and administration of medication.

Controversy exists about the effectiveness of different methods of emergency cardiac care because of wide variation in reported survival among centers[3], ranging from 0%[4] to 44%.[5] This variation may be attributable to differences in the type of EMS system, proportion of victims receiving bystander CPR, response time intervals of providers, or geography of the city in question.[6] Furthermore, different approaches to reporting survival make comparison of studies difficult.[6-8] A consensus conference has offered guidelines for uniform reporting of results to facilitate comparison of results.[2]

The purpose of this analysis was to estimate the relative effectiveness of the type and tier of an EMS system, unit response time interval of providers, and rate of bystander CPR on survival after out-of-hospital cardiac arrest. Using a protocol developed a priori, we performed a metaanalysis based on conventional techniques.[9,10] The protocol comprised selection criteria for the primary studies, definitions of the primary endpoints, and an analysis plan.[11] The metaanalysis was part of a larger cost-effectiveness analysis of improvements to EMS systems for out-of-hospital cardiac arrest. The results of the cost-effectiveness analysis are reported elsewhere.[12]

Definitions of terms The organization of an EMS system may vary both in the degree of training of the health care providers, as well as in the number of vehicles responding to a medical emergency. No universally accepted nomenclature exists for categorizing EMS systems, and some terms may have different meanings for different people.

To facilitate clarity and understanding, the following terms are defined. Emergency health care providers vary in the degree of their training and may or may not transport patients to the hospital. Basic life support (BLS) providers administer oxygen and CPR to victims of cardiac arrest. Providers of BLS with defibrillation (BLS-D) defibrillate patients using automated or manual defibrillators. Finally, advanced life support (ALS) providers are trained to perform endotracheal intubation and to administer IV medications. BLS or BLS-D level care may be provided by emergency medical technicians (EMTs) in ambulances or by firefighters in pump vehicles or vans. Generally, ALS care is only provided by EMTs in ambulances. These personnel are referred to by others as "paramedics."

The team that responds to a cardiac arrest in a given city may be part of a one-tier or two-tier EMS system. In a one-tier EMS system, a single provider and vehicle type responds to medical emergencies. In a two-tier system, two types of providers and/or vehicles respond. The vehicles may include ambulances, which respond from ambulance bases; or pump vehicles or vans, which respond from fire stations. In two-tier EMS systems, BLS providers (first tier) usually arrive more quickly because more generally are serving a community. In American cities with two-tier EMS systems, the second responding providers (second tier) have ALS capability. About 75% of the American urban population is served by a two-tier rather than by a one-tier EMS system.[14]

In this analysis we considered five configurations of EMS systems: (1) one tier with BLS providers, (2) one tier with BLS-D providers, (3) one tier with ALS providers, (4) two tiers with BLS followed by ALS (BLS + ALS) providers, and (5) two tiers with BLS-D followed by ALS (BLS-D + ALS) providers.

MATERIALS AND METHODS

Detailed descriptions of our methods are available from the US National Auxiliary Publication Service.[13]

Inclusion and exclusion criteria We identified articles published between 1966 and August 1992 using a comprehensive MEDLINE search for the keywords "heart arrest" with subheadings "therapy," "resuscitation," and "cardiopulmonary resuscitation," combined with "prognosis" or "survival." We then conducted a manual search of the bibliographies of all citations to check for previously unidentified articles. Only references published in the English language were considered. The authors of the primary studies were not contacted to identify additional studies.

All published primary studies, but not unpublished studies or abstracts, were considered for inclusion in the analysis. We included only studies in which the following systems were evaluated: one-tier BLS, BLS-D, or ALS; two-tier BLS + ALS; and BLS-D + ALS. Studies were included whether or not the first responding unit was ambulance- or fire company-based in a two-tier EMS system. We assumed that the base of origin would not affect the success of resuscitation, although the associated costs would be different.

The a priori exclusion criteria were EMS system type other than those of interest (ie, systems in which nurses or physicians arrive at the scene as ALS providers), patient population of fewer than 100 cardiac arrests, inability to determine the total number of cardiac arrests, and lack of data for survival to hospital discharge. When subjects were included in more than one publication from a single center, only the report with the largest number of subjects was included.

Data abstraction The following variables, when available, were recorded from each study: number of arrests of presumed cardiac origin, survival to hospital discharge, response time interval, proportion of bystander CPR, and type of EMS system. The response time interval of providers was defined as the mean response time interval, in minutes, between receipt of the call for aid and the arrival of providers at the scene. Bystander CPR was defined as CPR provided at the scene by laypersons.

For one-tier EMS systems, the only relevant response time interval was that of the single vehicle responding to the call. For two-tier EMS systems, the mean time interval before the arrival of each responding vehicle was available. However, only the response time interval of the first vehicle was used in the analysis as a measure of response performance in these systems. Therefore all subsequent mentions of mean response time interval refer to the mean time of arrival of the vehicle in a one-tier EMS system and of the arrival of the first response vehicle in a two-tier EMS system.

If the mean response time interval or rate of bystander CPR was not described or if the level of skills of the response crew was not explicitly stated, we requested the unpublished information or confirmation of the appropriate classification of the EMS system from the primary author. If only arrests due to ventricular fibrillation were reported, no attempt was made to obtain the total number of cardiac arrests from the authors. Studies reporting only arrest due to ventricular fibrillation were excluded from the analysis.

The articles were independently reviewed for eligibility and data abstraction (GN and IS). All differences were resolved by discussion (GN, IS, AL). Numbers were abstracted twice and checked for accuracy after data entry. Different systems described in a single article were treated as separate studies because the systems were operating in different areas or times and did not involve the same patients.

Primary analysis We used 'S' statistical software in our analysis.[15, 16] The planned initial analysis was to consider the effect of the independent variables proportion of bystander CPR, response time interval, and type of EMS system (whether the system was one-tier BLS, BLS-D, or ALS; or two-tier BLS + ALS or BLS-D + ALS) on the proportion of individuals surviving to hospital discharge. However, because of differences in the number of studies of each type of EMS system (eg, we had 12 studies of ALS and only two of BLS-D + ALS) and differences in the number of cardiac arrests among studies, this analysis yielded unstable estimates that were largely determined by individual studies. Therefore it was not possible to discriminate between different one-tier EMS systems (BLS versus BLS-D versus ALS) or between different two-tier EMS systems (BLS + ALS versus BLS-D + ALS). As a result, in the primary analysis we evaluated the effect of the independent variables proportion of bystander CPR, response time interval, and tier (the referent group one-tier EMS systems versus two-tier EMS systems) on the proportion of individuals surviving to hospital discharge. Studies with missing values for one or more of these variables were omitted from the primary analysis.

We used a generalized linear model because the outcome of interest was a binary response (alive at discharge, or not). Possible random effects were addressed by means of dispersion estimation.[17,18] The 'S' GLM procedure estimates the maximum likelihood with an iteratively reweighted least-squares algorithm.[16]

After including the main terms (response time interval, tier, and proportion of bystander CPR) in the model, we used a stepwise procedure to check for interactions among these variables.[16] This procedure checks for up to third-order interactions between terms, although only first-order interactions are usually examined. The criterion for entry of a term into the model or removal of a term from the model is based on minimization of the AIC statistic.[16] All the main terms (bystander CPR, response time interval, tier) and one interaction term (CPR by response) were retained.

Secondary analyses We conducted many secondary analyses to examine the robustness of the findings of the primary analysis. First, we added studies with missing values to the analysis by either replacing the missing values with the weighted group means (separated by tier) or with weighted least-squares estimates (not separated by tier) for the data available. There was one exception to the imputation of missing values. For one study in which median but not mean response time interval was reported[19], we used the median of 9 minutes to estimate response time interval rather than classify the value as missing. Because of the nature of the distribution of response time intervals in a system, the use of the median would have underestimated the mean response time interval.

We performed a secondary analysis by dropping the statistically significant interaction term for response time interval by CPR because the interaction was unexpected. We performed another secondary analysis with the effects of CPR and response time interval modeled nonlinearly (using Generalized Additive Models in 'S') to check for the adequacy of the linear model. Fifth, a secondary analysis was repeated with a variable indicating the presence or absence of ALS providers (paramedics) added to the data set. Finally, we performed an analysis with the ALS indicator variable but without the tier indicator variable.

We identified outlying studies by calculating Cook's D[15] statistic for each study. We identified potential overdispersion by plotting study size against residual for each study. Secondary analyses were performed without outliers or without influential studies that might support increasing overdispersion with increasing sample size. We checked for potential publication bias with the use of a funnel plot of effect size versus sample size.[20]

Terms of contract with sponsor The terms of the contract between the investigators and the sponsor were determined at the outset, after the investigators proposed the initial study design and methods. We reserved the right to control the methods and conclusions of the study and to publish the results of the study regardless of the outcome.

RESULTS

Literature review We identified 158 articles.[13] In 28 articles the EMS system was of a type other than the five of interest, in 9 the patient population comprised fewer than 100 cardiac arrests, in 48 we could not determine the total number of arrests of presumed cardiac origin, in 5 data on survival to hospital discharge were lacking, and in 32 articles patients had been included in more than one article. Thirty-six articles describing 41 systems met the criteria for inclusion in the analysis. The nine studies excluded for having a patient population smaller than 100 cardiac arrests comprised 407 cardiac arrests.

The data abstracted from these articles are shown in Table 1. There were 9, 11, 12, 7 and 2 sets of data for one-tier BLS, BLS-D, ALS; and two-tier BLS + ALS, BLS-D + ALS systems, respectively. These articles described EMS systems in six countries and were published between 1973 and 1992. The total number of cardiac arrests varied from 100 to 4,216, and the mean rate of bystander CPR ranged from 0% to 49% (overall mean, 25%). The mean response time interval ranged between 4.0 and 18.0 minutes in one-tier ambulance systems. The outlying mean response time intervals were observed in one-tier BLS systems. A narrower range of mean response time intervals was observed in one-tier ALS systems. In two-tier BLS + ALS, and BLS-D + ALS systems, the mean response time interval varied between 2.0 and 4.8 minutes for first response, and 5.0 and 11.2 minutes for the paramedics (overall mean, 5.7 minutes). Survival to hospital discharge varied from 0 to 21% (overall mean, 8%). Survival was 5.2% in a one-tier EMS system or 11.9% in a two-tier EMS system. Complete data were available for thirty-two systems after contacting the primary authors.

The articles included in this analysis were all case series. Four randomized controlled trials were identified[55-58], but none met our a priori inclusion criteria. One reported only results on patients subjected to autopsy[55], another only reported data on patients in ventricular fibrillation[56], one described a system other than those of interest[57], and one lacked survival data.[58]

Primary analysis Greater survival to hospital discharge was associated with shorter response time intervals ($P<.01$) or with a two-tier EMS system as opposed to a one-tier EMS system ($P<.01$) (Table 2). Surprisingly, the coefficient for the proportion of patients receiving bystander CPR was negative ($P=.04$). However, the interpretation of the effect of CPR is complicated by the statistically significant positive interaction between the proportion receiving bystander CPR and the response time interval ($P=.02$). A point estimate and confidence intervals for survival in an EMS system may be calculated from Table 2 by substitution of the proportion of bystander CPR and response time interval.

The absolute change in probability of survival to hospital discharge was calculated for incremental changes in each variable after adjustment for other variables (Table 3). Using the overall mean proportion of bystander CPR (25%) and overall mean response time interval (5.7 minutes) for the studies analyzed, fitted survival was 5.2% within a one-tier EMS system or 10.5% within a two-tier EMS system. A 1-minute decrease in mean response time interval was associated with an absolute increase in survival of .4% in a one-tier EMS system, or .7% in a two-tier EMS system. A 5% increment in bystander CPR was associated with an absolute increase in survival of .1% in a one-tier or two-tier EMS system with overall means as above.

Secondary analyses We obtained results similar to those of the primary analysis when we imputed missing values with weighted group means or with weighted least-squares estimates or if the analysis did not include a term for the interaction between bystander CPR and response time interval (results of secondary analyses available from National Auxiliary Publication Service.[13] Nonlinear modeling yielded graphs of independent variables versus fitted values similar in shape to those of the primary analysis. Therefore models of quadratic or higher order were not considered.

A secondary analysis using both parameters for "tier" and "ALS" did not yield a model different from the primary analysis (ie, ALS was not significantly associated with survival and did not enter into the model). Another secondary analysis with a parameter for ALS providers

Table 1.
Data abstracted from the literature

City	No. of Cardiac Arrests	EMS System	Bystander CPR (%)	Mean Respons Time (Minutes)*	Mean Second Response Time (Minutes)†	Survival to Discharge (%)
Durham, North Carolina[21]	126	BLS	28.5	6.5		8.7
Reykjavik, Iceland[22]	222	BLS	40.5	7.3		9.5
Halifax[23]	114	BLS	20.2	5.3		7.0
King County, Washington[24]	321	BLS	19.0	4		5.6
Winnipeg[25]	849	BLS	24.0	18		3.9
Arrowhead, Minnesota[26]	118	BLS	37.1	6.5		2.5
Vancouver[27]	110	BLS	30.0	5.7		3.6
Odense[28]	160	BLS	13.0	—		5.3
Ontario[29]	754	BLS	16.2	7.8		2.1
Stockholm[30]	307	BLS-D	15.0	7.8		3.6
Stockport, England[4]	113	BLS-D	38.0	4.5		0
Nottinghamshire, England[19]	403	BLS-D	44.7	9		10.9
Iowa[31]	110	BLS-D	20.0	5.7		10.9
Milwaukee[32]	566	BLS-D	49.0	7.1		6.4
Arrowhead, Minnesota[26]	116	BLS-D	32.0	6.5		5.2
Brighton, England[33]	216	BLS-D	15.0	16		2.3
Rochester, Minnesota[34]	100	BLS-D	35.0	—		6.0
Stockholm[35]	109	BLS-D	27.0	8		2.8
Odense[28]	148	BLS-D	15.0	—		1.4
Ontario[29]	756	BLS-D	19.0	7.6		2.9
New Westminster, British Columbia, Canada[36]	224	ALS	—	—		8.5
Pittsburgh[37]	187	ALS	21.0	5.97		9.6
Los Angeles[38]	294	ALS	38.0	5		10.2
Lucas, Kent, Southfield counties, Michigan[39]	3849	ALS	20.0	4.73		7.0
Vancouver[27]	244	ALS	14.0	5.7		11.5
Chicago[40]	3221	ALS	24.9	8		1.7
Torrance, California[41]	112	ALS	0	—		13.4
West Yorkshire, England[42]	1196	ALS	31.0	6.4		5.4
Cincinnati[43]	147	ALS	—	—		15.0
St Louis[44]	243	ALS	31.0	5		4.5
Royal Oak, Michigan[45]	244	ALS	—	—		9.1
South Glamorgan, England[39]	108	ALS	11.0	6		5.6
Milwaukee[47]	4216	BLS + ALS	—	2	5	12.6
Lincoln, Nebraska[48]	169	BLS + ALS	—	—	—	20.7
Tucson[49]	372	BLS + ALS	29.8	4.1	5.1	5.9
Seattle[50]	600	BLS + ALS	22.4	3.4	5.1	8.6
Minneapolis[51]	514	BLS + ALS	15.0	4.6	6.5	16.1
King County[52]	349	BLS + ALS	20.0	2.7	7.7	17.2
Tucson[53]	298	BLS + ALS	28.9	3	5	8.4
Seattle[50]	687	BLS-D + ALS	25.9	3.2	5.1	13.9
King County[54]	321	BLS-D + ALS	61.0	4.8	11.2	12.8

Dashes denote that data were unavailable from the original article or its primary author.
*In BLS + ALS and BLS-D + ALS, response time of the first vehicle.
†Response time of the second vehicle in BLS + ALS and BLS-D + ALS systems.

in place of that for tier yielded an additional interaction term (Appendix 1). Not only is the interpretation of this model difficult, but the estimates of fitted absolute and incremental survival obtained from such a model are counterintuitive (Appendix 2). This model suggested a survival of 12% in a non-ALS system, which lacks face validity. The association of greater survival with increasing CPR rather than with decreasing response time contradicted the widely accepted concept of a "chain of survival."

Secondary analyses performed without studies identified as influential[25, 36, 47] or as outliers[39, 40] yielded effect estimates, SEs, and test statistics similar to those of the primary analysis.[13] The funnel plot did not demonstrate evidence of publication bias.

In summary, although minor differences in results were discerned during the secondary analyses of the effectiveness data, the effect estimates, their SEs, and graphs of the independent variables versus the fitted values were quite similar to those of the primary analysis. The mean and 95% confidence intervals for effect estimates for each main parameter in each of these secondary analysis were essentially coincidental with those of the primary analysis.[13] Furthermore, analysis of residual diagnostics did not suggest lack of fit. None of the secondary analyses supported any clinically relevant or important changes to the primary analysis.

DISCUSSION

On the basis of the articles analyzed, fitted survival was 5.2% in a one-tier EMS system or 10.5% in a two-tier EMS system. A decrease in response time interval and the use of a two-tier as opposed to a one-tier EMS system were each significantly associated with increased in survival to hospital discharge. For the changes considered, changing to a two-tier from a one-tier EMS system offers substantially greater increases in survival than a 1-minute decrease in response time interval in either system (absolute difference of 5.3% versus .4% or .7%).

This analysis supports the need for a chain of survival to improve survival after out-of-hospital cardiac arrest, as endorsed by the American Heart Association[59]: early access, early bystander CPR, early defibrillation, and early ALS consisting of intubation and IV medication. The significance of response time interval corresponds in part to the first link in the chain. The significance of the provision of two-tiered response corresponds to the provision of integrated EMS services for cardiac arrest (ie, early access, early defibrillation, and early ALS). Increases in bystander CPR, the second link, were of small benefit (absolute change in survival of .1% for each 5% increment) relative to the benefit of differences in other components of the EMS system. The analysis does not have sufficient power to discriminate between provision of early access and of early defibrillation.

Other authors have drawn attention to the need to report survival after out-of-hospital resuscitation in a consistent manner.[2,7,8] Many centers have had difficulty reproducing the stellar results of Seattle and King County, Washington.[3] Rather than focus on the results of a single center, metaanalysis provides more generalizable evidence of effectiveness than may be obtained from a single study. This analysis pooled published survival estimates for out-of-hospital cardiac arrest. A priori inclusion criteria were used to determine the eligibility of studies for this analysis. Where possible, additional data were obtained from the primary authors to enlarge the size of the data set available for analysis. Adjustment for differences in EMS system, response time interval, and proportion of bystander CPR allowed for estimation of the relative influence of each component on survival.

Table 2.
Parameter estimates for log odds ratio of survival to hospital discharge.

Features	Effect	SE	F	P
Intercept	–.295	.852		
Bystander CPR (%)	–7.273	3.45	5.45	.04
Response time inverval (minutes)	–.402	.14	8.69	<.01
Tier (–1, 1)*	.384	.23	10.17	<.01
Interaction of CPR response	1.322	.54	5.76	.02

Residual deviance, 216; *df* 27.
*Indicator variable coded as –1 for one-tier and 1 for two-tier EMS systems.

Table 3.
Fitted absolute and incremental survival.

Features	One-Tier EMS System	Two-Tier EMS System
Absolute survival (%)	5.2	10.5
Incremental survival with 1-minute improvement in response time interval (%)	.4	.7
Incremental survival with 5% increase in bystander CPR (%)	.1	.1

Since our analysis was performed, additional studies have emphasized the poor results of resuscitation in some large cities served by EMS systems. A two-tier BLS-D + ALS system in New York City obtained an overall survival to hospital discharge of 1.4%.[60] Thirty-two percent of victims received bystander CPR. The median response time interval was 9.9 minutes. A one-tier ALS system in Chicago obtained an overall survival of 1.8%.[61] Twenty-one percent of victims received bystander CPR. The median response time interval was 6 minutes. A recent prospective study failed to show any improvement in survival with the presence of ALS providers rather than BLS-D providers in a one-tier system with similar provision of bystander CPR and response time interval.[62] Together, these results corroborate the findings of the present analysis, and reinforce the importance of rapid response. Also, the finding of significant differences in survival between the black and white communities indicates the potential influence of factors unrelated to EMS system on survival.[61] Data describing such potentially significant demographic information were not available from the studies analyzed. However, the random-effect model used in the analysis would compensate in part for such potential differences between studies.

With this analysis it was not possible to estimate the relative influence of different types of one- tier EMS systems (eg, BLS versus BLS-D versus ALS) or of different types of systems of two-tier EMS systems (eg, BLS + ALS versus BLS-D + ALS). Therefore the analysis neither supports nor refutes the relative importance of intubation and IV medication as links in the chain of survival. Interestingly, Cummins et al[59] estimated no difference in survival between a one-tier BLS-D system and a one-tier ALS system or between a system of two-tier BLS + ALS and a system of two-tier BLS-D + ALS. More recently, Kellerman et al[63] evaluated the effect of substitution of BLS-D for BLS in a two-tier EMS system in a controlled clinical trial. Early defibrillation was not associated with a statistically significant difference in survival (6.3% for BLS + ALS versus 9% for BLS-D + ALS, P=NS). These findings corroborate our inability to differentiate among one-tier EMS systems or among two-tier EMS systems.

A recent metaanalysis discriminated between BLS and BLS-D providers in one-tier and two-tier EMS systems.[64] However, the authors of the analysis failed to adjust for differences in response time interval and proportion of bystander CPR and grouped both one-tier and two-tier EMS systems together. Furthermore, they excluded some studies after the fact, relied only on studies published after 1980, and only considered ventricular fibrillation arrests. Each of these weaknesses would tend to yield an overestimation of the effectiveness of BLS-D relative to BLS providers.

Our findings differ from that of some other groups, who have found that the introduction of paramedics markedly improved survival. Cummins et al[59] estimated that a one-tier ALS system had a survival 5% greater than that of an one-tier BLS system. However, their averaging of results across centers did not adjust for differences in response time interval or bystander CPR.

Other parameters of potential interest include the age of the patients and the proportion of cardiac arrests with an initial rhythm of ventricular fibrillation or ventricular tachycardia. The vast majority of the studies analyzed did not report such data. Because the proportion of cardiac arrests with an initial recorded rhythm of ventricular fibrillation or ventricular tachycardia is strongly correlated with the response time interval, the nature of the rhythm is an intermediate outcome rather than an independent parameter.

Unfortunately, the data available for this analysis were suboptimal. Randomized controlled trials are recognized as the most valid estimate of the efficacy of an intervention. No randomized trials met our inclusion criteria. Therefore the studies used in this analysis were case series. They were largely published before the release of the recommendations of the Utstein consensus conference.[2] The two-tier systems were mostly from two geographic areas. Many studies of one- tier systems were old. Furthermore, the studies span many years. Complete data on all variables of interest (response time interval, percentage of bystander CPR, and percentage of individuals alive at hospital discharge) were only available in 32 of 41 studies (78%), despite extensive attempts to contact the authors of the studies. Response time intervals were highly correlated with the level of complexity of the EMS systems, being lowest in the most complex systems (BLS + ALS and BLS-D + ALS, Table 1). This makes it difficult to accurately determine the relative contributions of these two variables to any improvement in survival.

That response time interval and provision of two-tier EMS services were associated with significantly greater survival but the provision of defibrillation was not suggests that the provision of defibrillation may be less important than the provision of rapid response or the provision of integrated EMS systems with the capacity to quickly treat and transfer a patient to a hospital. Defibrillation and response time interval are closely correlated with the provision of a two-tier EMS system. In this metaanalysis we could not differentiate which intervention (defibrillation, intubation, or IV medication) was most important.

Alternatively, the nonsignficance of defibrillation may reflect some of the uncertainty associated with measurement of response time intervals. Valenzuela and Spaite and colleagues identified the potential difference between response time intervals and the time to the patient's side or the time to defibrillation.[65, 66] Collapse-to-intervention intervals were not available for this analysis but may be more representative of EMS system performance.

The minimal effect of bystander CPR may be attributable to its lack of importance relative to other factors. Alternatively, it may indicate the performance of bystander CPR in the absence of activation of EMS services (eg, not following American Heart Association guidelines for calling 911 before the initiation of CPR). Finally, it may merely reflect a lack of power, given the small number of studies relative to the number of variables considered.

The significant interaction between bystander CPR and response time interval may relate to a time-dependent phenomenon whereby the longer it takes for an EMS provider to arrive, the greater the chance that a bystander will arrive who is willing and able to perform CPR. Furthermore, it may represent an effect whereby bystander CPR in the absence of subsequent EMS providers is not associated with a substantial likelihood of survival.

Because this analysis is complex, we will now review the rationale for the assumptions that were made and discuss their implications. The first concerns the criteria used to decide whether to include a study of the effectiveness of EMS systems in the analysis. We excluded studies of systems in which nurses or physicians arrive at the scene as ALS providers because they are likely to be expensive, have not been demonstrated to be better than the systems we studied, and are not being contemplated for broad use in North America. We chose to exclude studies that only reported survival of patients with ventricular fibrillation because these patients clearly have a better survival rate than the average patient who has sustained a cardiac arrest. Furthermore, the EMS team responds to all arrests, not just those of individuals with ventricular fibrillation. Patients who survive only to hospital admission but not to hospital discharge have not benefited from resuscitation, and therefore we excluded studies that did not report survival to hospital discharge. We did not include any studies that reported the results of fewer than 100 victims of cardiac arrest, largely because the amount of data they would contribute to the analysis would not affect the results in any substantial way and out of concern that results from small centers may be associated with larger variances. Others have performed metaanalyses after a similar exclusion of smaller studies.[68] Finally, it was our judgment that the time needed to locate unpublished articles and articles not published in English did not justify the effort. When we derived a funnel plot, there was no obvious evidence for publication bias.

Our initial intent was to compare the effectiveness of five EMS systems: one-tier BLS, BLS-D, or ALS; two-tier BLS + ALS, or BLS-D + ALS. Unfortunately, the estimates of effectiveness were unstable, so we believed the results unreliable. We attributed this to the nonexperimental nature of the studies (no randomized trials), the heterogeneity of the systems evaluated (variations in the size and geography of the city, the rapidity of response, the skills of individuals with the same apparent level of training), differences in the frequency of bystander CPR, and the relatively small number of studies (only two studies of BLS-D + ALS). Of course, it is possible that there really is no difference in survival among systems, but we believed this unlikely. Further analysis of the data demonstrated a difference in survival among the first three systems and the last two (ie, one-tier EMS systems versus two-tier EMS systems.) This model was mathematically stable and seemed clinically sensible because it is acknowledged that one of the important feature of an EMS system is the provision of a rapid response (and the two-tier EMS systems were usually associated with the most rapid responses).

Concern may arise as to whether we misspecified the model of survival by using a parameter for "tier" rather than for "ALS." Formal tests of misspecification[68, 69] have been used in other settings as an aid in resolving this kind of modeling dispute. In our metaanalysis, it was quite clear that interstudy differences existed that were probably not due to chance. Because of this, we adopted a random-effects model. Paraphrasing Cox[70], this acknowledged that it was impossible to determine the causes of interstudy differences to appropriately model them. Instead, we made allowances for these differences by placing a probability distribution on them. Because there are many different ways of modeling random effects and little if any subject matter motivation or sample information to discriminate among them, it is likely that some misspecification of the random effects is unavoidable. More important is that even if we were sure about the correct form of the random effects model, its very use implies that something is misspecified (missing) in the fixed-effects model. This we believe would be impossible to separate out from other misspecifications of interest, given 32 residuals (ie, the number of studies with complete data) on which to base a formal test.

The analysis using an ALS parameter rather than tier parameter was not used as the main analysis for three reasons. First, there was an extra interaction term between ALS providers and response time interval. This implied that ALS providers were helpful if the response time interval was short and harmful if it was long. This complicated the analysis but also reemphasized the importance of response time interval which was evaluated in our primary analysis. Second, the response time interval used in the model was the response time interval of the first vehicle on the scene (there is only one response time interval in one-tier EMS systems). Therefore the response time interval in systems including ALS providers and a non-ALS first response would reflect that of the non-ALS team. Third, in only seven studies in which BLS + ALS or BLS-D + ALS was analyzed were data not missing for CPR or response time interval. The narrow distribution of mean response time interval of the second vehicle limited modeling of the effect of changes in second response time. Therefore the variability of the data, the stability (or lack thereof) of the statistical models evaluated, and clinical sense led us to use the primary analysis that we did.

In our study, 13% of the values for the rate of bystander CPR or response time were missing even after we contacted authors to obtain additional information. Imputation of missing values in a variety of ways did not substantially change the fitted values. Furthermore, after exclusion of influential studies the model was stable. The plotting of residuals against the number of cardiac arrests suggested that a more complicated random-effects model was not required.

Despite the limitations of the data described above, this analysis is the most comprehensive assessment of the effectiveness of different components of EMS systems for survival after out-of-hospital cardiac arrest. It offers generalizable estimates of the effectiveness of different EMS systems and adjusts for differences in response time interval or proportion of bystander CPR. In no other study have the results of different centers been pooled with the use of statistical analysis and adjusted for differences in response time interval or proportion of bystander CPR. Given the difficulty many centers have had in reproducing the results of the most effective centers, this metaanalysis represents an important advance.

The authors of future studies should adopt the data elements recommended by the Utstein consensus conference, and such studies should be of sufficient size to determine effectiveness in terms of survival to hospital discharge. Although randomized controlled trials are difficult to perform, every effort should be made to encourage experimental or quasi-experimental designs with some form of control group. Future studies should involve careful prospective follow-up of outcomes in a wide variety of settings, with stepwise introduction of new technologies (eg, firefighter first response followed by paramedics.) For example, a multicenter study of sequential introduction of rapid defibrillation followed by ALS providers is under way in Ontario, Canada.

In the absence of further evidence of effectiveness, consideration of relative costs may facilitate informed decisions about potential improvements to EMS systems. For example, use of firefighters responding from fire stations to provide the initial response in a two-tier EMS system rather than ambulance attendants responding from ambulance bases may provide improvements in survival at lower cost but equivalent effectiveness.[12]

In summary, evaluation of the effectiveness of different EMS systems for survival after out-of-hospital cardiac arrest is fraught with difficulties because of inadequate data. The effectiveness estimates derived in this analysis must be interpreted with caution because of the lack of randomized studies evaluating the effectiveness of different EMS systems and the heterogeneity of the data. More methodologically rigorous studies are necessary for policymakers to confidently estimate the consequences of their decisions regarding funding and expansion of complex EMS systems.

CONCLUSION

On the basis of a metaanalysis of data from 41 case series of resuscitation in out-of-hospital cardiac arrest, we conclude that decreased response time interval and the use of two-tier rather than one-tier EMS systems may each be associated with significantly greater survival. Prospective controlled trials should be performed to assess the relative benefit of interventions in two-tier EMS systems.

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Appendix 1.
Parameter estimates for secondary metaanalysis with ALS parameter in place of tier.

Features	Effect	SE	F	P
Intercept	–.621	.735		
Bystander CPR (%)	–5.311	3.01	3.61	.07
Response time interval (minutes)	–.462	.119	17.39	<.01
Paramedic (–1, 1)*	1.206	.258	23.73	<.01
Interaction (response×paramedic)	–.186	.037	26.52	<.01
Interaction (CPR×response)	1.127	.478	6.25	.02

Residual deviance, 149; *df*, 27.
*Indicator variable coded as –1 for no paramedic and 1 for paramedic system.

Appendix 2.
Fitted absolute and incremental survival for secondary metaanalysis with ALS parameter in place of tier.

Features	Non-ALS System	ALS System
Absolute survival (%)	12.7	16.1
Incremental survival with 1-minute improvement in response time (%)	–.06	5.6
Incremental survival with 5% increase in bystander CPR (%)	3.7	4.4