SPECIAL REPORT

Methodological Challenges in Studies Comparing Prehospital Advanced Life Support with Basic Life Support

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Conflicts of interest: none

Keywords: bias; confounding; epidemiology; study design

Abbreviations:
ALS: Advanced Life Support
BLS: Basic Life Support
ED: emergency department
EMS: Emergency Medical Services
GCS: Glasgow Coma Scale
ISS: Injury Severity Score

Received: May 9, 2016
Revised: August 19, 2016
Accepted: September 14, 2016

Online publication: April 3, 2017

doi:10.1017/S1049023X17000292

Abstract

Determining the most appropriate level of care for patients in the prehospital setting during medical emergencies is essential. A large body of literature suggests that, compared with Basic Life Support (BLS) care, Advanced Life Support (ALS) care is not associated with increased patient survival or decreased mortality. The purpose of this special report is to synthesize the literature to identify common study design and analytic challenges in research studies that examine the effect of ALS, compared to BLS, on patient outcomes. The challenges discussed in this report include: (1) choice of outcome measure; (2) logistic regression modeling of common outcomes; (3) baseline differences between study groups (confounding); (4) inappropriate statistical adjustment; and (5) inclusion of patients who are no longer at risk for the outcome. These challenges may affect the results of studies, and thus, conclusions of studies regarding the effect of level of prehospital care on patient outcomes should require cautious interpretation. Specific alternatives for avoiding these challenges are presented.

Li T, Jones CMC, Shah MN, Cushman JT, Jusko TA. Methodological challenges in studies comparing prehospital Advanced Life Support with Basic Life Support. ***Prehosp Disaster Med*****. 2017;32(4):444-450.**

Introduction

Emergency Medical Services (EMS) is a crucial component of the health care system. In 2010, there were 129.8 million emergency department (ED) visits in the United States, of which 21.2 million patients (16.3%) were transported by EMS.[1] Acute conditions requiring immediate medical attention, such as traumatic injury and stroke, are among the leading causes of mortality in the United States,[2] and thus, effective prehospital care is essential during medical emergencies.

Care delivered by EMS providers can generally be classified as either Basic Life Support (BLS) or Advanced Life Support (ALS).[3,4] The training and scope of practice for EMS providers vary tremendously by country, state, and community. However, in general, BLS providers complete a minimum of 110 hours of training and are trained to provide immediate, basic, life-saving care and transport for patients who activate the emergency response system.[5,6] Conversely, the training of ALS providers often exceeds 1,000 hours;[5-7] ALS providers are trained to provide the highest level of prehospital care, including: advanced assessments and interventions, such as intubation; 12-lead electrocardiogram monitoring and interpretation; manual defibrillation and cardioversion; needle decompression; and intravenous medication administration, among others.[5-7] In most communities, whether a patient receives BLS or ALS services depends on the severity of their illness or injury. Compared to BLS providers, the training of ALS providers is time-consuming and expensive; therefore, ALS is often a valuable and limited resource.[8] As such, it is important to mobilize the appropriate level of prehospital care to the scene of a medical emergency, and many communities use standardized emergency medical dispatching protocols to accomplish this goal. These protocols provide public safety dispatchers with a series of scripted questions to triage calls for medical assistance to determine whether ALS or BLS services should be dispatched to the scene;[9,10] ALS is more commonly dispatched to patients with more severe conditions, whereas BLS is more commonly dispatched to patients with less severe conditions.[8,11-13] However, it is also worth noting that not all communities use this type of dispatching; some communities do not have a tiered response system that separates BLS and ALS.[14]

Given that ALS services are limited and resource-intensive, there is a need to determine the appropriate level of care for patients in the prehospital setting.[15] The cost of staffing and equipping an ALS ambulance compared with a BLS ambulance is much higher and the training of ALS providers is lengthier than the training of BLS providers. If ALS care is not associated with improved patient outcomes compared to BLS care, it may not be cost-effective to train ALS providers. Indeed, some have questioned whether this additional training and cost is justified, and whether limited financial resources should be used to put more BLS ambulances in the field to increase coverage and reduce response times instead.[16]

Numerous studies have been conducted to examine the outcomes of patients treated by ALS providers compared with BLS providers; of these, many have concluded that ALS does not result in better patient outcomes compared with BLS.[17-19] A meta-analysis published in 2011 by Bakalos and colleagues concluded that ALS care for trauma patients is not associated with increased survival to hospital discharge compared with BLS care.[17] However, caution should be exercised when interpreting the results of studies comparing ALS to BLS care. Given the inherent challenges of conducting prehospital care research, many of these studies have limitations in their design and analysis that, until addressed, may preclude a definitive answer on the survival advantage of ALS versus BLS care. The objective of this special report is to describe five study design and analytic challenges often found in studies comparing ALS care to BLS care, and to discuss alternatives for each.

Report

Choice of Outcome Measure

Many studies have compared the effect of ALS with BLS care on patient survival.[17] Several types of survival can be examined as an outcome measure, including survival to ED arrival, survival to surgery, survival to hospital or intensive care unit admission, survival to hospital discharge, and neurologically intact survival at hospital discharge. Survival to hospital discharge is commonly the outcome of choice in this area of research,[19-23] as it can be argued that this outcome represents the ultimate clinical question as to whether patients recover or not. However, survival to hospital discharge may not be the most ideal outcome to model when attempting to determine the effect of ALS care compared with BLS care for several reasons.

First, patient survival to hospital discharge is a very distal outcome measure that may be influenced by several factors that are independent of the care received in the prehospital setting. For example, care provided in the ED may contribute to survival to hospital discharge. Specialized centers, such as trauma or stroke centers, may be able to provide care that increases survival compared with non-trauma or non-stroke centers. Second, survival to hospital discharge may be influenced by delay to surgical intervention after arrival to the ED.[24] Third, distance from the scene of the emergency to the ED may affect survival; closer proximity to the ED may account for observed increased survival.[24] Lastly, post-surgical care, such as cardiac rehabilitation, may also influence patient survival.[25,26] All of these factors are associated with survival to hospital discharge and may also be associated with ALS or BLS care, and thus, the association of interest may be confounded.

Although long-term outcomes may be preferable to measure in some instances, more proximal measures can be directly attributed to care provided by EMS providers. For example, survival to ED arrival is a more proximal outcome that is directly affected by prehospital care. Other more proximal alternative outcome measures include: ED length of stay, admission to the hospital versus discharge from the ED, admission to the hospital floor versus intensive care unit, and improvement in vital signs.

Logistic Regression Modeling of Common Outcomes

The effect estimate of interest in health research is often the relative risk, defined as the probability of the outcome in the exposed group divided by the probability of the outcome in the unexposed group.[27] In the current discussion, the relative risk is defined as the probability of survival (or mortality) in the ALS (exposed) group divided by the probability of survival (or mortality) in the BLS (unexposed) group. In studies where the relative risk cannot be computed directly, such as in case-control studies, the odds ratio is commonly used to approximate the relative risk.[28] When the outcome of interest is rare (<10%), the odds ratio approximates the relative risk.[27,29] However, when the outcome of interest is common (>10%), the odds ratio over-estimates the relative risk.[28-30]

Logistic regression modeling is an analytic method that estimates odds ratios in studies with dichotomous outcomes.[31,32] Since logistic regression modeling yields an adjusted odds ratio instead of an adjusted relative risk, the odds ratio can be used as an approximation of the relative risk when the outcome of interest is rare.[28] However, log-binomial regression modeling may be more appropriate in studies where the outcome of interest is common.[27,29-31,33]

Log-binomial regression and logistic regression are similar in that both are used for the analysis of dichotomous outcomes.[27] In contrast to logistic regression modeling, which yields an estimate of the adjusted odds ratio, log-binomial regression modeling yields an estimate of the adjusted relative risk.[27] Some have commented that the use of logistic regression modeling to estimate odds ratios in studies with common outcomes is not justified because log-binomial regression modeling can be used to directly estimate the relative risk.[30,33]

Survival is generally common in studies of trauma patients, as high as 93% in one study[34] and 81% in another.[35] Logistic regression modeling is the more common analytic method used;[16,17] however, the choice of outcome variable to model (survival) is usually common, resulting in an over-estimation of the relative risk.[28,29,36] Therefore, authors who choose to use logistic regression should model the outcome that is less common because the odds ratio from the logistic regression model will be a better approximation of the relative risk. If a particular outcome is more preferable to model than the other, such as survival instead of mortality, and that outcome is common, log-binomial regression may be more appropriate.

Baseline Differences and Confounding

There are inherent differences between patients who receive ALS or BLS care. Most communities use emergency medical dispatching protocols that are designed such that dispatchers can identify patients with emergencies of higher acuity so that ALS providers can be dispatched to these patients and BLS providers can be dispatched to patients with emergencies of lower acuity.[9,10] Because higher-acuity patients have higher probability of mortality and lower-acuity patients have higher probability of survival, it may falsely appear that patients who receive ALS care survive less frequently than patients who receive BLS care. Therefore, ALS and BLS patients are difficult to compare, since BLS patients have an inherent survival advantage.[24] Thus, to the extent that these baseline differences are not controlled, higher mortality among ALS patients is expected and the survival difference between these two groups of patients may be the result of confounding rather than the level of prehospital care provided.[24]

To illustrate, in a study that evaluated the impact of ALS and BLS care on cardiac arrest patients, the authors concluded that ALS care did not increase the proportion of patients surviving to hospital discharge compared with BLS care.[23] In this study sample, the proportion of patients with asystole was higher in the ALS group compared with the BLS group (84% versus 72%).[23] As patients with asystole survive infrequently, the higher mortality in the ALS group compared with the BLS group is expected, without controlling for baseline differences. Similarly, in a study that compared outcomes of penetrating trauma patients who received ALS care versus BLS care, the authors concluded that ALS care did not benefit patients in their sample.[20] There were substantial differences between patients who received ALS care compared with patients who received BLS care in this study that placed the ALS patients at higher probability of death than the BLS patients. There were more patients who had gunshot wounds in the ALS group compared with the BLS group (73% versus 62%), more ALS patients who had pulseless electrical activity compared with BLS patients (17% versus 4%), and ALS patients, on average, had lower Glasgow Coma Scale (GCS) scores compared with BLS patients (11.7 versus 13.2). These baseline differences indicate that patients in the ALS group had greater physiologic compromise compared with patients in the BLS group, and thus, the probability of mortality among the ALS patients is expected to be greater compared with BLS patients.

The issue of baseline differences between ALS and BLS patients is one of confounding. Confounding, the mixing of effects between an exposure, an outcome, and a third variable,[37] is a common concern in observational studies and can lead to spurious effect estimates.[38] Traditional observational studies compare outcomes between groups with different exposures; confounding becomes a problem when the groups under study differ in known and unknown ways other than the exposure.[38] One type of confounding is confounding by severity, in which not only the disease that forms the indication for treatment is a confounder, but the severity of the disease is also a confounder.[39]

If the receipt of ALS or BLS care is the exposure of interest and patient survival or mortality is the outcome of interest, injury or illness severity confounds the association between ALS or BLS care and survival or mortality (Figure 1). As shown in Figure 1, any observed increase in survival or mortality associated with receiving ALS or BLS care may be explained by severity of injury or illness. Since emergency medical dispatching protocols are used to optimize the mobilization of EMS providers to scenes of emergencies such that patients with severe injuries or illnesses receive ALS care, patient outcomes may be influenced by severity. Therefore, confounding by severity is a major concern in any study attempting to estimate the effect of level of prehospital care on patient outcomes when patients receive differential resources (ALS versus BLS, or ground versus air ambulance) based on their initial complaint. Patient outcomes may not be attributed to the level of prehospital care received but may be attributed to injury or illness severity.

Many studies address the issue of confounding through multivariable regression modeling. Variables such as age, sex,

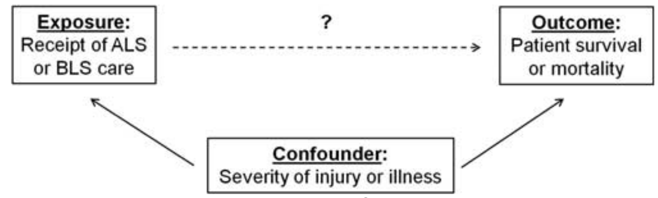

Figure 1. Confounding by Severity.
Note: Solid arrows represent proposed causal effects between variables and the dotted-line arrow with a question mark represents the casual effect of interest. Here, severity of injury or illness is a confounder of the association between receipt of ALS or BLS care (exposure) and patient survival or mortality (outcome).
Abbreviations: ALS, Advanced Life Support; BLS, Basic Life Support.

cardiac rhythm, vital signs, Injury Severity Score (ISS), and GCS score are commonly included as covariates in regression models. Despite controlling for these potential confounders through regression modeling, there is potential for measurement error, and therefore residual confounding. For example, the assignment of ISS to injured patients may be subjective, as identical injuries may be assigned different scores by different raters. One study found that the inter-class correlation coefficient for inter-rater reliability of the ISS was 0.49 (range: 0.19-0.85).[40] Therefore, whether ISS is a reliable indicator of anatomic injury severity is questionable. Regardless of its reliability, however, there is great variation in the way ISS can be handled in the analysis, as ISS can be treated as a continuous variable[20] or a categorical variable.[34,35] Additionally, different cut points can also be used to categorize ISS.[34,35] The categorization of continuous variables may lead to measurement error and residual confounding, resulting in biased effect estimates.[41,42] The use of GCS encounters similar challenges, as some have commented that the GCS lacks criterion-related, construct, and content validity, and thus, should not be regarded as a valid clinical or research tool to quantify level of consciousness.[43] In a study assessing the inter-rater reliability of the GCS, the agreement percentage for total GCS was only 32% and has similarly been used as a continuous or categorical variable.[43] The low reliability of the ISS and GCS may lead to measurement error, limiting the ability to control for confounding during the analysis.[44] Therefore, although methods of controlling for baseline differences between the two groups of patients are commonly used, the existence of residual confounding and unmeasured confounders cannot be reasonably excluded.

Other advanced statistical methods to control for confounding exist, including propensity scores and instrumental variable analysis; however, these methods are not commonly used in studies comparing ALS and BLS care.[18,19,37,45,46] To the authors' knowledge, only two studies evaluating the effect of level of prehospital care on patient outcomes have used propensity scores and instrumental variable analysis methods.[18,19]

Although the use of propensity scores appears to be a promising method to adjust for observed confounding, it is essential that the same theoretical framework used to select covariates to include in regression models, namely the inclusion of only confounders and not colliders or intermediates, be applied when selecting covariates to use in the estimation of propensity scores (further discussed in the next section). Compared with propensity scores, instrumental variables have the potential to adjust for observed and unobserved

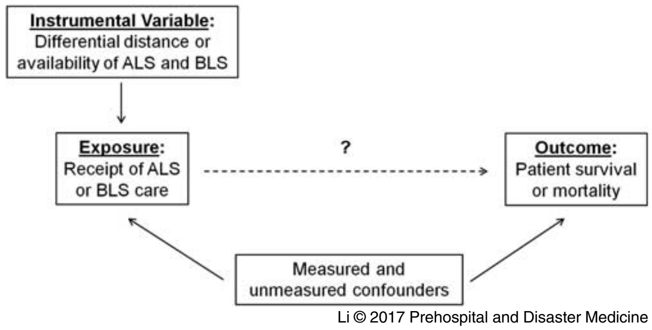

Figure 2. Differential Distance or Availability of ALS or BLS as an Instrumental Variable.
Note: Solid arrows represent proposed causal effects between variables and the dotted-line arrow with a question mark represents the causal effect of interest. Here, differential distance or availability of ALS and BLS is an instrumental variable for the association between receipt of ALS or BLS care (exposure) and patient survival or mortality (outcome).
Abbreviations: ALS, Advanced Life Support; BLS, Basic Life Support.

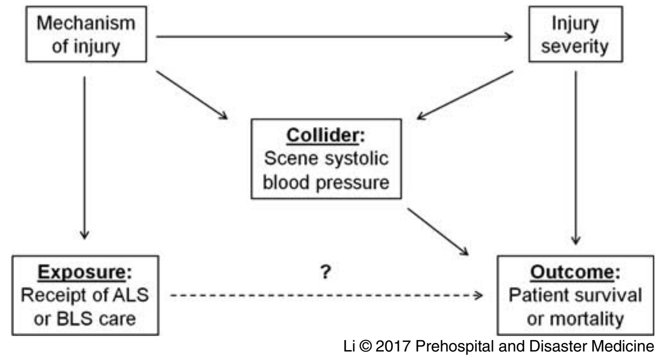

Figure 3. Simplified Causal Diagram of a Collider Variable.
Note: Solid arrows represent proposed causal effects between variables and the dotted-line arrow with a question mark represents the casual effect of interest. Here, scene systolic blood pressure is a collider in the *exposure – mechanism of injury – scene systolic blood pressure – injury severity – outcome* pathway because scene systolic blood pressure is associated with mechanism of injury and injury severity.
Abbreviations: ALS, Advanced Life Support; BLS, Basic Life Support.

confounding.[47] An instrumental variable is a variable that is: (1) associated with the exposure; (2) not associated with confounders, both observed and unobserved; and (3) not associated with the outcome, other than through its association with the exposure.[48-50] The identification of a valid instrumental variable is challenging because the assumption that the instrumental variable is not associated with the outcome, independent of treatment, is not directly testable.[49]

As an illustrative example, McConnell and colleagues utilized instrumental variable analysis to assess whether patients with head injuries transferred from Level III, IV, and V trauma centers to Level I trauma centers have reduced mortality compared with those transferred to Level II trauma centers.[51] Previous studies assessing the association between transfer to a Level I or Level II trauma center and mortality in patients with head injuries have failed to show a benefit of Level I trauma center care compared with Level II trauma center care.[51] In the study by McConnell and colleagues, differential distance between the nearest Level I and Level II trauma centers was used as an instrumental variable.[51] Distance between the nearest Level I and Level II trauma center was chosen because it is associated with being transferred to that trauma center, not associated with confounders, and not independently associated with survival, thus meeting the definition of an instrumental variable. Applying the instrumental variable method, McConnell and colleagues found that patients with head injuries transferred to Level I trauma centers had improved survival compared to patients transferred to Level II trauma centers.[51]

Similarly, the differential distance between the nearest ALS or BLS unit to a patient, or availability of ALS or BLS to respond to a patient, may be appropriate for use as an instrumental variable in studies comparing ALS and BLS care on patient survival. As shown in Figure 2, differential distance or availability of ALS or BLS is associated with whether a patient receives ALS or BLS care (exposure), but is not independently associated with patient survival or mortality (outcome), and does not appear to be associated with measured or unmeasured confounders.

After the identification of an instrumental variable, a variety of methods can be used for analysis, including probit structural equation models, 2-stage logistic models, and generalized method of moments estimators.[52] However, limitations are noteworthy and it is important to consider the assumptions of instrumental variables as well as the difficulties of finding a strong instrumental variable when there is strong confounding.[47,48,50]

Inappropriate Statistical Adjustment

Due to concerns of confounding, it is common for researchers to enter covariates that are potential confounders, based on informal arguments or statistical procedures, into their multivariable regression models to adjust for confounding.[53] However, these methods of selecting covariates do not differentiate between confounders and colliders.[53] By definition, a confounder is a variable that is a common cause of both exposure and outcome, which should be adjusted for to reduce confounding bias.[54] On the other hand, a collider is a variable that is caused by two other variables.[54-57] For example, in Figure 3, scene systolic blood pressure is a collider on the *exposure – mechanism of injury – scene systolic blood pressure – injury severity – outcome* pathway. Despite meeting typical statistical criteria for confounding (ie, statistically associated with exposure and outcome),[54,58] adjusting for a collider variable can induce, rather than reduce, bias in certain situations; this type of bias is known as "collider bias."[54,59-62] Interested readers are referred to Cole et al[59] and del Junco et al[56] for more detailed discussions of collider bias.

Furthermore, some variables entered as covariates into regression models are intermediates; that is, variables on the causal pathway between the exposure and outcome. Adjustment for intermediates to estimate direct effects requires additional assumptions that may not be satisfied, specifically the absence of unmeasured confounding for the exposure and outcome, and the absence of unmeasured confounding for the intermediate and outcome.[63] Figure 4 is a simplified causal diagram of the association between level of prehospital care (ALS or BLS) and survival

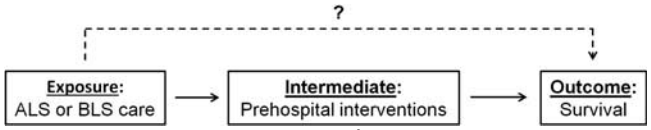

Figure 4. Simplified Causal Diagram of an Intermediate Variable in the Association between ALS or BLS Care and Survival.
Note: Solid arrows represent proposed causal effects between variables and the dotted-line arrow with a question mark represents the causal effect of interest. Here, prehospital intervention is an intermediate variable in the association between ALS or BLS care and patient survival.
Abbreviations: ALS, Advanced Life Support; BLS, Basic Life Support.

with an intermediate variable (prehospital interventions) that is commonly adjusted for in the literature.

In Figure 4, the variable "prehospital interventions" is not a confounder of the association between level of prehospital care and survival because level of prehospital care precedes prehospital interventions and prehospital interventions is on the causal pathway of the exposure and outcome. Given that prehospital interventions is an intermediate, rather than a confounder, there is no need to adjust for prehospital interventions, and adjustment to estimate direct effects requires further assumptions that may not be met.[63]

Therefore, to appropriately adjust for confounding, relationships between variables may best be visualized in a causal diagram using a directed acyclic graph before entering them into regression models.[53] Once variables and causal associations are displayed in a causal diagram, it may become apparent that certain variables are actually colliders or intermediates and should not be included as confounders in multivariable regression models.

Inclusion of Patients Unlikely to Survive

In addition to confounding, some studies of prehospital level of care and patient outcomes include patients who are essentially dead on arrival.[20,21,23] Some have commented that patients in cardiac arrest before arrival to the hospital are essentially dead;[24] this is especially true for patients with pulseless electrical activity or asystole. The probability of survival after pulseless electrical activity or asystolic cardiac arrest is extremely low.[64,65]

Therefore, authors should consider excluding patients with pulseless electrical activity or asystole in the prehospital setting from their analysis because patients who are dead before the arrival of EMS providers are no longer at risk for mortality or survival; these individuals no longer contribute person-time to the risk set. Consequently, including these patients in the analysis may result in the spurious association that ALS care increases the risk of mortality. Sensitivity analyses would be helpful in determining the effect of excluding these patients from the analysis; for example, conducting the primary analysis including these patients and then a second analysis excluding these patients. Inclusion of findings from such sensitivity analyses in a manuscript would illustrate how the estimated associations might differ depending on sample selection. This analytic approach would increase transparency and allow readers to draw inferences based on thorough consideration of sample characteristics and differences that may arise depending on the underlying source population to which results are being generalized.

Discussion

The public relies on EMS providers during medical emergencies; therefore, determining the effect of differing levels of prehospital care is critical. It is reasonable to believe that ALS providers, who receive more intensive training and have at their disposal advanced interventions compared to BLS providers, can provide care that leads to better prognosis for patients with severe injuries or medical conditions. However, the vast majority of studies regarding prehospital level of care and patient outcomes have failed to find an association between ALS care and improved patient outcomes, and thus challenge face validity.[16-20]

This report outlined five frequent methodological and analytic considerations when conducting prehospital research on patient outcomes: the choice of outcome measure; the use of logistic regression to model common outcomes; baseline differences between study groups (confounding); inappropriate statistical adjustment; and inclusion of patients who are no longer at risk for the outcome. To date, no review has collectively synthesized all of these challenges. This report also offered potential alternatives to address these challenges through the use of: different outcome measures; log-binomial regression modeling; the use of instrumental variables and propensity scores; using causal diagrams to differentiate between confounders, colliders, and intermediates; and carefully excluding patients who are no longer at risk for the outcome of interest.

There is no doubt that studies of the effect of prehospital care on patient outcomes are difficult to design and conduct. In light of these challenges, researchers are often forced to utilize non-randomized study design methodologies to draw conclusions on the effectiveness of ALS care compared to BLS care. These methods, and their associated analyses, have their own inherent challenges and limitations that may not allow an accurate reflection of causal inference or association. Thus, despite the outstanding work to date, results from original studies, systematic reviews, and meta-analyses on the level of prehospital care and patient outcomes should require cautious interpretation.

Results from double-blind, randomized, controlled clinical trials comparing the outcomes of patients treated by ALS and BLS providers would enhance causal inference.[15] However, randomized controlled clinical trials that randomize patients to receive ALS or BLS are rare due to the uncontrolled prehospital setting and acuity of patients that may make research procedures difficult.[15] Further, many institutional review boards or ethics committees may be hesitant to approve such randomized controlled trials. Given this, the true effect of level of prehospital care on patient outcomes remains to be elucidated. Researchers and readers should be aware of the methodological and analytic challenges that result from such non-randomized studies.

Conclusion

Many studies suggest that, compared with BLS care, ALS care is not associated with increased patient survival or decreased mortality. This report discussed common methodological challenges in studies that examine the effect of ALS, compared with BLS, on patient outcomes. These challenges may substantially affect the results of studies, and thus, conclusions of studies regarding the effect of level of prehospital care on patient outcomes should require cautious interpretation.

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