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variables: prehospital intubation and mortality

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## Abstract

We highlight the role of local instrumental variable (LIV) methods in exploring treatment effect heterogeneity using an empirical example of evaluating the use versus non-use of prehospital intubation (PHI) in patients with traumatic injury. We find evidence that effect of PHI on inpatient mortality vary over levels of unobserved confounders giving rise to a phenomenon known as *essential* heterogeneity. Under essential heterogeneity, the traditional instrumental variable (IV) method, when using a continuous IV, estimates an effect that is an arbitrary weighted average of the causal effects for marginal groups of patients whose PHI receipt are directly influenced by the IV levels. Instead, the LIV methods estimate the distribution of treatment effects for every margin and allows for predictable aggregation to recover estimates for meaningful treatment effect parameters such as the Average Treatment Effect (ATE) and the Effect on the Treated (TT). LIV methods also allow exploring heterogeneity in treatment effects over levels of observed confounders. In the PHI analysis, we estimate an ATE of 0.322 (se=0.16, p=0.04) and a TT of 0.046 (se=0.07, p=0.61). We find strong evidence of positive self-selection in practice, whereby patients who were most likely to be harmed by PHI were also less likely to receive PHI. However, the degree of positive self-selection mitigates in regions with higher rates of PHI use. We also explore factors associated with the prediction of significant harm by PHI. We provide clinical interpretation of results and discuss the importance of these methods in the context of comparative effectiveness research.

Key words: Instrumental variables; local IV methods; heterogeneity; prehospital intubation; mortality.

## Introduction

With enriched resources available for conducting comparative effectiveness research (CER) in the United States and the continuous development of more comprehensive observational databases based on electronic medical records, statistical and econometric methods for estimating treatment effects are in great demand. Treatment effects are the primary parameters of interest in comparative effectiveness research, albeit some effects are more useful for linking results to decision making within health care than others. Since the goal of CER is to help make better decisions within health care [1], two fundamental requirements arise in the development of such methods: 1) the treatment effect parameters reflect the needs of the specific decision maker in question, and 2) the estimates for these parameters carry a causal interpretation.

In this paper, we explore the comparative effectiveness of prehospital intubation (PHI) compared to no PHI on inpatient mortality following traumatic injury among patients who reached the emergency department alive. The safety and efficacy of PHI in trauma patients is controversial; there are currently no definitive guidelines as to when it is better to perform intubation at the scene by first responders, or to defer definitive airway management until after arrival at a hospital to facilitate the most rapid conveyance to advanced medical care. A registry-based retrospective cohort study demonstrated increased risk of death and long-term disability in patients with severe traumatic brain injury (TBI) who were intubated prior to arrival to the hospital, compared to those intubated in the emergency department (EDI) [2]. In contrast, the largest single-center study, comparing PHI to EDI, demonstrated no significant difference in rates of ventilator associated pneumonia or death [3]. It was suggested that the results, contrary to those of prior retrospective cohort studies demonstrating a higher incidence of pneumonia in prehospital-intubated patients, may have been influenced by a well-established, standardized paramedic rapid sequence intubation training program with continuous quality improvement measures.

The problem with these studies, as is widely recognized as the fundamental challenge of estimating treatment effects from observational data, is selection bias. Selection bias (i.e., confounding by indication) arises when factors that can influence the treatment choice, such as patient health, resource availability and provider skills, also influence outcomes. The significance of this well-known limitation was famously illustrated in the case of hormone replacement therapy in post-menopausal women. As several large-scale observational studies consistently showed these treatments to be effective for preventing chronic cardiovascular disease, hormone replacement therapy was widely adopted. Use then plummeted when these studies were eventually disproven by a large randomized trial [4]. It has been shown

subsequently that the reason for the discrepant results was that the observational studies failed to consider certain confounders such as socioeconomic status [5] or failed to distinguish initiation of therapy from prevalence of therapy [6]. The significance of overcoming the limitations of common observational study designs cannot be overstated as it could lead to fewer mistaken conclusions regarding treatment effectiveness and a greater use of sound observational studies to develop the evidence base of comparative effectiveness research. Unfortunately, a study with a randomized design, which can ideally overcome these selection biases, may be logistically and/or ethically challenged in the context of many crucial clinical questions, including the case of when to perform intubation in patients with traumatic injury. Even in the case of the only RCT performed to date in a traumatic brain injury population, blinding as to the treatment group amongst providers was not possible (as the intubation could not be concealed), potentially affecting the results of the study [7].

In order to address selection bias, in line with what a pragmatic randomized design should have accomplished, we will focus our attention to the use of instrumental variables (IV). In what follows, we highlight the role of traditional and newer IV methods in comparative effectiveness research, substantiated with evaluating the effectiveness of prehospital intubation using these methods.

## **Overview of Instrumental Variable Methods and Interpretation of Results**

Instrumental variable (IV) methods have been a cornerstone method for observational studies in the economics literature and its origins date back to the 1920s [8]. In the last couple of decades, these methods have gained popularity in the medical literature on the evaluation of alternative medical treatments [9,10,11,12,13], the types of evaluations that were by and large restricted to clinical trials. The instrumental variables determine or affect treatment choice, but do not have a direct effect on outcomes, except to the extent that they influence the choice of treatment [14,15,16]. Thus, by using IVs, one can induce substantial variation in the treatment variable, but have no direct effect on the outcome variable of interest. One can then estimate how much of the variation in the treatment variable induced by the instrument—and only that induced variation—affects the outcome measure. In econometric terminology, this induced variation is called the exogenous variation and identifies the desired estimate. These analyses constitute an important body of work that have advanced the field of CER by going beyond establishing associations between treatments and outcomes to estimating causal effects of

treatments on outcomes, such as a RCT conducted on a similar population can inform. The adoption of these techniques for CER, although limited thus far, appears to be accelerating.

### *Non-essential heterogeneity*

The field of CER is also devoted to estimating heterogeneity in treatment effects [17]. In the presence of treatment effect heterogeneity, however, results from traditional IV approaches may suffer from lack of interpretability. An IV estimate of treatment effect using standard methods (e.g. two-stage least squares) is comparable to that arising from an RCT only under the assumption that treatment effects are constant for everyone in the population with the same observed characteristics. Even if treatment effects are allowed to be heterogeneous, IV estimates assume patients or their physicians do not have any additional information beyond what the analyst of an observational data possess that can enable them to anticipate these effects and select into treatment that would potentially give them the largest benefits. In other words, unobserved confounders are assumed not to be moderators of treatment effects (this situation is denoted as non-essential heterogeneity [20]).

An underlying data generating mechanism for non-essential heterogeneity is illustrated with a stylized example of potential outcomes in Figures 1(a) and 1(b). In these figures, the X-axis represents levels of an unobserved confounder, while the Y-axis represents the potential outcomes. The line connecting the '+'s represents the schedule of potential outcomes in the population had every patient received the control treatment. As constructed, people respond differently to the same treatment. This is called response heterogeneity. The line connecting circles represent the schedule of potential outcomes for the same people had they received the new treatment. Although there is also response heterogeneity from the new treatment, the differential responses across alternative treatments (denoted by the grey bars in Figure 1(a)) are held constant across people. That is, treatment-effect heterogeneity is constant across levels of the unobserved confounders. Technically, treatment-effect heterogeneity is denoted as non-essential only when it is statistically independent of response heterogeneity.<sup>1</sup> Figure 1(b), illustrates how IVs produce interpretable results in this situation. In practice, we do not observe the potential outcomes under both treatments for each patient. Rather, we observe outcomes for a self-selected group of patients receiving each treatment. An IV helps match the unobserved level of confounding. Therefore, an IV compares outcomes for a treated and an untreated group of patients, whose treatment choices are driven by the levels of the IV, and

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<sup>1</sup> Note that for non-essential heterogeneity, there should be full independence between response and treatment effect heterogeneity, and not just mean independence.

hence the levels of their unobserved confounders are held fixed at some arbitrary value defined by the specific instrument used [18]. For example, an analyst using distance to treatment facilities as instruments would, in effect, hold the levels of unobserved confounding fixed at a specific level, which may be different than the level held fixed by another analyst using physician preferences as instruments. However, with non-essential heterogeneity, the level of unobserved confounder at which an instrument is ‘acting’ is inconsequential, since each IV will estimate the constant treatment effect, which is also the average treatment effect in the population. The interpretation of IV estimates in such a situation is straightforward.

### *Essential Heterogeneity*

When unobserved confounders moderate treatment effect in a systematic fashion, treatment effect heterogeneity depends on response heterogeneity, and becomes known as *essential heterogeneity*. This is illustrated in Figure 1(c). Since the marginal patients identified by an IV are entirely dependent on the specific instrument being used and how this instrument affects treatment choices [15, 16], the use of different instruments by different analysts will produce different treatment effects because they represent the effects for different groups of marginal patients, and IV results become instrument dependent. This key insight, originally highlighted by Heckman [19], is that it is difficult to interpret and apply IV results to clinical practice, where patients are often believed to select treatment based on their idiosyncratic net gains or preferences. In response to this insight, most traditional IV methods estimate a Local Average Treatment Effect (LATE). This estimate is often substantially different from mean treatment effect concepts such as the Average Treatment Effect (ATE).

A new genre of IV methods originally developed by Heckman and colleagues [20,21,22] directly addresses these limitations of traditional methods. Known as local instrumental variable (LIV) approaches, these methods can relax assumptions, allow unobserved characteristics of patients that influence treatment choices to also be moderators of treatment effects, and recover the full distribution of treatments effects across all possible margins of patients choices, not just the one directly influenced by an IV, by explicitly developing a choice model for treatment selection. This choice model tries to explain choices based on all observed risk factors and also all possible IVs that are identified in the data, so that for each predicted level of probability for treatment choice, we observe some patients who choose treatment and some who do not. One can then study how the difference in average outcomes, the marginal treatment effect (MTE), between these two groups varies over levels of the probability of

treatment choice (Figure 1(d)). This approach, known as the local instrumental variable (LIV) approach, uses control function methods to identify the MTEs and subsequently combines them to form interpretable and decision-relevant parameters of interest such as the ATE or the Effect on the Treated (TT) or the Untreated (TUT). ATE estimates the average gain if everyone undergoes treatment as compared to an alternative treatment or no treatment at all. This has been one of the most popular parameters of interest for health economists and policy analysts when making inference about health care policies [23]. Treatment Effect on the Treated (TT) estimates the average gain to those who actually select into treatment and is one ingredient for determining whether a given treatment should be shut down or retained as a medical practice or in the formularies. It is informative on the question of whether the persons, choosing the treatment, benefit from it in gross terms. For CER, there is strong theoretical reasoning for why a treatment effect that is averaged over all patients in a population, i.e. the Average Treatment Effect (ATE), can mislead patient or physician decision making, ultimately affecting welfare in this population [24,25,26]. Therefore, more nuanced subgroup specific effects, represented by conditional MTEs, are often more useful.

An LIV method can confirm if the assumption of non-essential heterogeneity is valid. It also provides a seamless approach to explore treatment effect heterogeneity across observed confounders. Recently, Basu et al. [27,28] applied these methods to estimate ATE, TT and MTEs of breast cancer treatments on costs and mortality. A detailed description of the theory and methods on LIV approaches as it relates to CER can also be found in these works.

In this paper, we apply traditional IV and LIV approaches to estimates interpretable treatment effects and also to explore heterogeneity in effects of the use of prehospital intubation compared to emergency department intubation on inpatient mortality following traumatic injury.

### **Clinical Context of Prehospital Intubation and Mortality**

Patients who sustain injuries are susceptible to aspiration and loss of airway due to decreased level of consciousness, whether due to direct head trauma or other severe injury resulting in shock. Prevention of secondary brain injury by avoidance of hypoxia and hypotension is a primary goal in the initial treatment of head trauma, and early intubation has been advocated to facilitate improved oxygenation [29]. However, in 2007, an expert panel concluded that there was not sufficient data to promote the standard practice of PHI for patients with traumatic brain injury [30]. These recommendations were based on the available data, including multiple single-

center retrospective analyses with opposing conclusions as to the harm or benefit of PHI. For example, a review of severely head injured patients in a statewide trauma registry revealed a 4-fold adjusted risk of death for PHI versus emergency department intubation [2]. Although the authors contend they had employed the best available risk-adjustment methods including propensity scoring, unobserved differences in the two groups may have influenced the decision to intubate as well as the observed outcomes. A single prospective observational study of prehospital rapid sequence intubation in 209 patients matched to historical non-intubated controls concluded PHI was associated with increased mortality, possibly due to inadvertent hyperventilation, transient hypoxia, or longer time at scene prior to transport [31]. Accordingly, the panel suggested that all of the studies considered failed to account for potentially important confounders, among the many methodological issues that hampered their ability to definitively recommend for or against PHI [30]. It concluded that a randomized control trial was one of the main goals for future investigation.

While not impossible to accomplish, because of the time-critical factors and the subject's inability to consent to randomized treatment, out-of-hospital clinical trials necessitate waiver of consent and are among the most highly regulated studies. This level of scrutiny may be, at least in part, the reason it took four years to enroll only 312 patients, despite 1045 screened, in the only randomized controlled trial of prehospital intubation in adult patients with severe head injury reported to date [7]. It is widely recognized that RCTs may not allow for real-world conduct of treatments in these settings, and may significantly vary from what is possible or practical to perform in practice. In the study by Bernard et al [7], patients who did not receive rapid sequence intubation medications were excluded. Even in employing the most-highly trained paramedics already certified to perform advanced airway management, the study required an additional 16 hours of airway management training for study participants to learn rapid sequence intubation techniques. It has been previously reported that in addition to training and maintenance of skills, ongoing quality assurance is required for successful administration of a PHI program [32]. Whether prehospital trauma provider systems adopt such measures will undoubtedly be impacted by resource availability and the perceived potential benefit to the patients served.

The effect of PHI may vary over numerous factors, many of which cannot be measured due to the current limitations of prehospital data collection and reporting. Variability in the success of PHI may be influenced by patient factors (both pre-existing and injury-related conditions), provider skill level and/or experience in decision making, resource availability, and environmental constraints at the scene of injury. We set out to explore heterogeneity in

comparative effects across both the observed and unobserved factors that also may have played a role in the choice of intubation in practice. We use data from the National Study on Costs and Outcomes in Trauma (NSCOT) for this purpose. The planned analyses of this data examined variation in care delivery between level I trauma centers and non-trauma centers, determined the extent to which differences in care correlate with patient outcome (including major functional outcomes at 3 and 12 months after injury), and estimated acute and 1-year costs, describing the relationship between costs and effectiveness for trauma and non-trauma centers [47,33,34,35,36,37,38,39]. As a rich source of prospectively collected observational injury-related data, the NSCOT has also been used for a number of secondary analyses, beyond the originally intended scope of the study [40,41]. In 2007, Bulger and colleagues used the NSCOT data to demonstrate significant variation in the conduct of out-of-hospital treatments [42]. The authors observed variation in the rates of endotracheal intubation across regions, ranging from 5% to 48% of all patients treated, and noted that the variation persisted after stratification by severity of injury, suggesting that this wide range in practice was not dependent upon patient injury heterogeneity observed across regions. To date, an IV analysis has never been used on this data. Moreover, the comparative effects of PHI versus no PHI on inpatient mortality have rarely been studied in trauma patients, with most retrospective analyses focusing on the comparison between patients intubated in the field prior to arrival at the hospital to those intubated in the emergency department.

### Theory of Local Instrumental Variable (LIV) Approach

The theory of local instrumental variable (LIV) approach starts with a formal model for choices. Let the net (latent) utility for treatment,<sup>2</sup>  $\Lambda$ , based on which choices are determined,<sup>3</sup> is given as

$$\Lambda = \mu_\Lambda(X, Z) + U_\Lambda \quad E(U_\Lambda) = 0 \quad D = I(\Lambda > 0), \quad (1)$$

where  $X$  represents a vector of observed confounders and  $Z$  represent a vector of instrumental variables.  $U_\Lambda = \Lambda - \mu_\Lambda(X, Z)$  has expectation of zero while  $I(\cdot)$  is an indicator function representing treatment choice  $D$ . Equation (1) expresses the typical random utility framework for discrete choices in econometrics [43,44]. Following this framework, one can write  $D = I(\Lambda > 0) = 1(U_\Lambda > -\mu_\Lambda(z, x)) \Leftrightarrow 1(F_{U_\Lambda}(U_\Lambda) > F_{U_\Lambda}(-\mu_\Lambda(z, x))) \Leftrightarrow 1(F_{U_\Lambda}(U_\Lambda) > 1 - P(z, x))$  where

<sup>2</sup> Latent utility in this framework is an anticipated form of utility rather than an experienced form and implicitly accounts for decision maker's preferences which varies over all factors. A factor cannot affect treatment choice unless it affects this latent utility.

<sup>3</sup> Decision maker in the intubation context is likely the paramedic attending the trauma patient.

$P(z,x) = F_{U_A}(\mu_A(z,x))$  and  $F_{U_A}(U_A) = U_D \sim Uniform(0,1)$  by construction. The formulation in (1) decomposes factors that determine choice of treatment into the observed and unobserved components (again, by the analyst). The additive separability of (1) in terms of observables and unobservables plays a crucial role in the justification of instrumental variable methods [20,22]. Hereon, we denote  $S(z,x) = 1 - P(z,x)$ . Consider for simplicity the single instrument case, i.e.  $Z$  is a scalar rather than a vector of instruments. Given model (1) and the assumed independence of  $Z$  and  $U_V$ , changing  $Z$  externally from  $U_V$ , shifts all people in the same direction (towards or against  $D = 1$ ). This produces “monotonicity” in the sense of Imbens and Angrist [18].

If  $Y_1$  and  $Y_0$  represent the potential outcomes for a patient with treatment and control respectively, the treatment effect for that patient is denoted as  $\Delta = Y_1 - Y_0$ . A Marginal Treatment Effect (MTE) [45,16,20] is the average gain to patients who are indifferent between receiving treatment 1 versus treatment 0 given  $X$  and  $Z$ . These are the patients at the margin as defined by  $X$  and  $Z$ . Formally, MTE can be defined as:

$$\begin{aligned} MTE(x,z) &= E(\Delta | X = x, Z = z, \Delta = 0) = E(\Delta | X = x, U_A = -\mu_A(z,x)) \\ &= \mu_1(x) - \mu_0(x) + E(U_1 - U_0 | U_A = -\mu_A(z,x)) \\ &= \mu_1(x) - \mu_0(x) + E(U_1 - U_0 | U_D = S(z,x)), \end{aligned} \quad (2)$$

where the last equality follows from the fact that  $S(Z,X)$  is a monotonic transformation of the mean utility  $\mu_V(Z,X)$  while  $U_D$  is a monotonic function of  $U_A$ . The mean conditional treatment effect at each level of  $U_D$  is the value of the MTE at that level of  $U_D$ . Evaluation of the MTE parameter at low values of  $U_D$  averages the outcome gain for those individuals whose unobservable characteristics make them less likely to undergo treatment, while evaluation of MTE parameter at high values of  $U_D$  gives the gain for those patients with unobservable characteristics which make them more likely to undergo treatment. For example, a local average treatment effect (LATE) [15] is a weighted sum of all MTE within the margin at which LATE is identified. In the limit, as  $\mu_V(z',x) \rightarrow \mu_V(z,x)$ , LATE converges to MTE under standard regularity conditions [20,22].

An additional feature of MTE is that all mean treatment effects parameters, including the Average Treatment Effect (ATE), Effect on the Treated (TT), and the traditional IV effect, can be calculated from weighted averages of MTE. These weights can be obtained from the data at hand [22,27,46]. For example, the ATE is the sum of all MTE across all distinct values of  $U_D$ , weighted equally (conditional on  $X$ ).

If MTEs do not vary over  $U_D$ , it provides direct evidence on the absence of essential heterogeneity. In such a situation, the conditional MTEs converge to the conditional ATE or the TTs. One can then solely focus on exploring treatment effect heterogeneity across observed confounders.

### *Estimators for MTEs and other mean treatment effect parameters*

The method of local instrumental variable can be used to identify and estimate the MTE over the support of the propensity score, estimated using IVs in the choice equation, for selecting treatment [20,22,46]. Specifically, the rate of change of the mean outcome with respect to  $P(Z)$  evaluated at a particular value of  $S(z, x) = 1 - P(z, x)$  gives

$$\begin{aligned} \frac{\partial}{\partial P(z, x)} E(Y | Z = z, X = x) \bigg|_{1 - P(z, x) = u_D} &= E((Y_1 - Y_0) | X = x, u_D = 1 - P(z, x)) \\ &= E\{\Delta | X\} + \frac{\partial K(P(z, x))}{\partial P(z, x)} = \text{MTE}(x, u_D) \end{aligned} \quad (3)$$

where  $E\{\Delta | X\}$  is the average treatment effect conditional on  $X$  and  $K(P(z, x))$  is a differentiable function of  $P(z, x)$ . A formal derivation is given in the Appendix. Equation (3) shows that the key element for the estimation of MTE is the function  $K(P(z, x))$ . This function can be estimated using different econometric techniques, such as using flexible approximation to  $K(P(z, x))$  based on a polynomial of the propensity score in a regression estimator or using fully non-parametric matching techniques. Specifically, in a regression context, equation (3) is implemented by regressing the outcome  $Y$  on all covariates, the estimated propensity score  $\hat{P}(z, x)$ , the interaction of the propensity score with all covariates, and a polynomial on the propensity score, as needed, to fully capture the non-linearity of the outcome with respect to  $P(Z)$ . One then computes the partial derivative of the regression estimand with respect to the propensity score to get an LIV estimand that estimates the MTEs.

## Methods

### *Data*

The National Study on Costs and Outcomes in Trauma (NSCOT) was a prospective observational cohort study of trauma treatment at 27 Level 1 trauma centers and 124 non-trauma hospitals in 15 US regions, including both urban and suburban centers [47,48]. The 15 regions were defined by one or more contiguous metropolitan statistical areas (MSA) in 14 states. Subjects enrolled were treated for moderate to severe injury at participating hospitals between July 2001 and November 2002. Among the major exclusion criteria were patients who arrived at the hospital without vital signs and those pronounced dead within 30 minutes of arrival to the hospital. Further details about the selection criteria and sampling methodology have been previously described [47,48].

For the purpose of the analysis described herein, the NSCOT data were restricted to a subset of patients whose injury was severe enough that advanced airway management was a reasonable possibility during the acute out-of-hospital resuscitation phases (ISS $\geq$ 16). This was primarily based on the range of severity of illness in a review of the available evidence in a published clinical practice guideline from the time proximate to the study period [49]. Indeed, the rate of PHI in patients with ISS<16 was less than 2% in the NSCOT data. We did not use inclusion criteria according to “need” for endotracheal intubation because there are no validated definitions, scales, or prediction rules for this characteristic. Furthermore, while a Glasgow Coma Score (GCS) of <9 is generally used as an indication for intubation, it was not used as an inclusion criterion in the current study because the time of GCS measurement with respect to drug administration (including muscle relaxants associated with rapid sequence intubation protocols) was not clear, suggesting that GCS might be a result of the treatment rather than an indication for it. We also restricted the study population to those patients transported directly from the scene of injury to the hospital by either air- or ground-based prehospital medical providers. Failed PHI attempts (n=101, 19% of all PHI) were included in the PHI group, even if they were subsequently intubated in the emergency department (n=80).

The available dataset allowed us to account for a variety of confounders, including patient demographics, pre-injury health insurance status, and clinical characteristics such as presence of prehospital shock, presence of severe head injury (as measured by Head Abbreviated Injury Scale score  $\geq$ 3), admission to a trauma center, and injury severity score (ISS) categories. Among the potential unobserved confounders were skill level and experience of provider performing intubation [50,51], scene characteristics that might make intubation particularly

difficult (such as intubating in awkward positions, dangerous situations or in a moving vehicle), ability of the provider to sense the need for intubation (e.g., medics have been previously been shown to be able to reliably predict whether someone has aspirated [52]), and unmeasured injury status.

The instrumental variable used was the rate of PHI per metropolitan statistical area (MSA). We computed this variable from the same dataset as our analyses data. However, for each patient, the level of PHI use in that patient's MSA was calculated after excluding that patient from both the numerator and the denominator. The IV was expected to be predictive of PHI intubation use for individual patients— higher use of this procedure in an MSA would be associated with higher likelihood of the index patient undergoing PHI if treated in that region. The rates are also expected to be independent of the potential outcomes in the overall target population, as they are mostly driven by system-level resources and practice guidelines. However, among patients receiving PHI, patients in high PHI use area may have different levels of unobserved confounders than those living in a low use area. This creates dependence between the instrumental variable and the unobserved confounders among those receiving PHI, even if they are independent in the overall population. If treatment effects are heterogeneous over these unobserved confounders, the situation of essential heterogeneity arise, and the traditional IV effect estimates the effect for a marginal group of patients with a very specific level of the unobserved confounder.

### *Statistical Analysis*

First, a naïve logistic regression analysis, controlling for observed levels of confounders, was run to study the adjusted effects of PHI. Various goodness of fit tests were used to ensure that the specification fit the data well.

Next, a traditional two-stage residual inclusion (2SRI) approach was applied using instrumental variables [53]. In the first stage, a logistic regression was used to predict the propensity to undergo PHI as a function of both observed confounders and the instrumental variables. A residual was computed by subtracting that predicted propensity score ( $\hat{p}(x,z)$ ) from the treatment indicator. In the second stage, another logistic regression was used to model the death indicator as a function of the PHI, observed confounders and the residual computed in the first stage. The treatment effect was computed based on the difference in predicted

probability of death between PHI and no-PHI. Standard errors were obtained using 1000 clustered bootstrap replicates.

Finally, the local instrumental variables (LIV) approach was employed. In the LIV approach, the logistic outcome regression was run on all covariates ( $X$ ), the estimated propensity score ( $\hat{p}$ ), the interaction of propensity score with all covariates, and a polynomial on the propensity score,  $K(\hat{p}; d)$ :

$$E(Y) = \text{Logit}^{-1}(\beta_0 + X \cdot \beta_1 + X \cdot \hat{p} \cdot \beta_2 + K(\hat{p}; d)) \quad (4)$$

The degree of polynomial,  $d$ , was selected based on likelihood-ratio tests between nested models with different degrees of polynomials for ( $\hat{p}(x, z)$ ). The derivative ( $dE(Y)/d\hat{p}$ ) of the final polynomial formulation was used as our LIV estimand to predict  $\text{MTE}(x, u_D)$ :

$$\hat{\text{MTE}}(x, u_D) = \left. \frac{dE(\hat{Y})}{dp} \right|_{p=u_D=(1-\hat{p}(x, z))}$$

The predicted values of the propensity score allow us to define the values of  $U_D$  over which MTE can be identified [54]. The larger the support of the propensity score, the bigger the set over which MTE can be recovered.

The dimensionality of  $X$  was reduced by using deciles of the estimated linear predictor ( $X \cdot \hat{\beta}_2$ ) in the LIV estimand that is only a function of the  $X$  and not the propensity scores.<sup>4</sup> These deciles are denoted as  $\eta_q$  hereon, where  $q = 1, 2, \dots, 10$ . Thus, using our coefficient estimates from the above regression (equation (4))  $\text{MTE}(\eta_q, u_D)$  were estimated by varying  $u_D$  between 0 and 1 and using average predicted  $\text{MTE}(x, u_D)$  for each  $\eta_q$ . Note that MTE estimates using a value of  $P(Z, X) = p$  are associated with  $u_D = (1 - p)$ . Using the empirical joint density of  $(\eta_q, u_D)$ , which also represents the weights for  $\text{MTE}(\eta_q, u_D)$  required to calculate the empirical ATE (estimated over the observed common support), we estimate the  $\text{MTE}(u_D)$ .

Next, we calculate the weights associated with ATE, TT and IV effect and use them to construct the respective treatment effect estimates. Standard errors for  $\text{MTE}(u_D)$  and all the mean treatment effect parameters are estimated via 1000 bootstrap replicates. All analyses were weighted using probability weights and accounted for clustering of patients by hospitals.

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<sup>4</sup> This is implemented by predicting  $X \cdot \hat{\beta}_2$ , where  $\hat{\beta}_2$  corresponds to the estimated coefficients on the interaction term of  $X$  and  $P(Z, X)$  in the LIV outcomes regression.

## Results

There were 2169 patients in the NSCOT data who met all the inclusion criteria. Of them, 514 (23.7%) were intubated prior to arriving in the emergency department of the hospital where they received definitive care (PHI). Table 1 illustrates the differences in observed levels of potential confounders. Compared to non-PHI patients, patients who underwent PHI were on average 8 years older, but were less likely to be 65 years and older, were more commonly identified as racially White, and on Medicaid. A higher proportion of patients who underwent PHI had prehospital shock, severe brain injury but no Charlson comorbidity. PHI was also associated with the highest category of injury severity scores. There was no difference in the rate of PHI vs. no-PHI by gender or by admission to trauma center.

Table 2 reports the estimated mean treatment effects based on different estimators. The naïve logistic regression analysis, controlling for observed levels of confounders produced a treatment effect estimate of 0.188 (se = 0.04, p < 0.001). It indicates that after controlling for observed confounders, on average, PHI increases in-patient mortality by 18.8% compared to no-PHI.

Next, the instrumental variable methods were evaluated. The instrumental variable was found to be a significant predictor (p < 0.0001) of PHI. In order to explore whether, at the least, the observed confounders distributed uniformly over the levels of the instrumental variables (a necessary test), we predicted the propensity of PHI as a function of IV only and then compared the levels of observed confounders above and below the median of this predicted propensity. Because a good instrument does not affect outcomes directly, it should considerably reduce the imbalance in levels of all confounders across the propensity median compared to the imbalances across treatment receipts. Table 1 reports the p-values for these comparisons on observed confounders and shows that the imbalance across levels of observed confounders were drastically reduced. Though not sufficient, this necessary test supports our theoretical assumptions that the imbalances in the levels of unobserved confounders should also be reduced across predicted propensity scores and the instrument should not directly affect outcomes.

The 2SRI approach estimated the treatment effects to be 0.029 (se = 0.09, p = 0.45) (Table 2). This estimate was about one-sixth of what was obtained via the naïve logistic regression. It says that the causal effect of PHI compared to no-PHI will increase in-patient mortality by 3%, which is not statistically significant from zero. This IV effect however, may not correspond to any interpretable mean treatment effect parameter if essential heterogeneity is present. To explore this, the local instrumental variable approach was used.

With the local instrumental variable approach, there was strong evidence of essential heterogeneity. Figure 3(a) shows how the marginal treatment effects vary over the latent dimension of unobserved confounding. This is analogous to the stylized situation depicted in Figures 1(c) and (d). Levels of unobserved confounders that made patients highly likely to undergo PHI are also associated with negative treatment effects or reduced mortality from PHI versus no-PHI. Similarly, levels of unobserved confounders that made patients less likely to undergo PHI are associated with positive treatment effects or increased mortality from PHI versus no-PHI. This provides strong evidence of self-selection behavior; that is, in practice, patients who were undergoing PHI were most likely to be benefiting from it. Consequently, the mean treatment effect parameters estimates were found to be substantially different than either the naïve or the traditional IV estimates (Table 2). The average treatment effect was estimated to be 0.322 (se = 0.16, p = 0.04), while the effect on the treated was estimated to be 0.046 (se = 0.07, p = 0.61). It indicates that had PHI been conducted on all trauma subjects, the average inpatient mortality rate would have increased by 32.2% points when compared to the situation where all trauma patients undergo no PHI. However, this estimate may be misleading because such an all-or-none approach is hardly a pragmatic comparison. Perhaps, more relevant is the estimate for the effect on the treated, which indicates that those who are undergoing PHI in practice could have reduced their average mortality rate by 4.5% had they not been subjected to PHI. This estimate, however, did not reach statistical significance.

Finally, treatment effects heterogeneity was explored based on observed confounders. Figure 3(b) illustrates the average treatment effects conditional on the decile of the portion of the linear predictor in the LIV estimand that is composed of the observed confounders. It was found that about 30% of the patient in our sample, which corresponds to 16% of the patient population (after weighting), would have experienced significant increase in mortality had they undergone PHI versus no-PHI. These patients constitute the *extensive margin* [26] of the comparison. Observed factors associated with this group were explored using a logistic regression on an indicator variable that took a value of one for patients who belong in this group. Table 3 presents these results. We found that older patients, patients with fewer comorbidities, males, non-Hispanic Blacks, patients on Medicaid, without prehospital shock or severe head injury, with lower ISS scores and those going to a non-trauma center were associated with significantly greater harm from PHI than no-PHI. As evident from Table 1, many of these characteristics also predicted non-receipt of PHI proving strong evidence of positive self-selection in practice.

Obviously, not all patients who belong in the extensive margin and could potentially get hurt due to PHI, ended up not receiving PHI. Among PHI recipient population, 12.8% could have

experienced significant decrease in mortality had they not undergone PHI. In order to understand characteristics associated with increased mortality with PHI among those who were undergoing PHI, another logistic regression was employed. Table 4 reports these results. The factors were similar to those predicting harm from PHI in the overall population (Table 3), however among PHI recipients, age, comorbidities and gender were no longer significant predictors of harm.

We also explored whether areas with higher PHI use were associated with less positive self-selection. That is, we wanted to know whether subjects who received PHI in lower use regions were less likely to be harmed by PHI than those who received PHI in higher use regions. We compared regions where PHI use rates were lower than the median rate versus regions where they were higher. Table 5 reports the results. We find compared to the risk of harm by PHI among the entire population, the risk of harm by PHI among PHI recipients is significantly reduced in low use areas ( $p = 0.02$ ), but not in high use areas ( $p = 0.07$ ), the difference in risk reduction between low and high use areas being significant ( $p = 0.003$ ). These results provide strong evidence of over-use of PHI in high-use regions.

## Conclusions

With the increased investment in developing large observational studies for comparative effectiveness studies, methods that produce valid and interpretable results are in great demand. Moreover, as the field of CER moves towards a patient-centered paradigm, understanding heterogeneity in comparative effects becomes crucial. In this paper, we have highlighted the recent development of instrumental variable methods to address such challenges. We applied these methods towards a substantive problem of evaluating the comparative effectiveness of prehospital intubation versus no prehospital intubation on inpatient mortality in trauma patients.

As the field moves more towards patient-centered approach, and especially trying to align these analyses to decision making in practice, one critical step is to be able to measure variables/confounders that are also readily available at the point of decision making, so that conditioning on them is pragmatic. We attempted to select variables that would be readily available for decision making from the start of care in the prehospital setting. Demographics are fairly easy to assess by observation. Calculation of the ISS score is time consuming and requires information not available to formally assess the extent of injury during the initial evaluation of the patient, but broad categorization of injury severity (mild, moderate, severe, near fatal) would

be possible in the moments prior to definitive prehospital treatment. Furthermore, severe head injury with decreased level of consciousness is estimable, and prehospital shock (as defined by systolic blood pressure<90 mmHg) is measureable. It is less likely that sufficient history would be known to estimate the patient's comorbidities or pre-injury insurance status. The admission to a trauma center is likely a result of the decision making made at the scene, but may have been directed by preliminary reports of the level of injury and facilitated specialized prehospital care from the outset. As prehospital electronic data management improves, better capture of scene data may inform development of more specific mortality risk assessment. With real-time decision support, the prehospital provider may be able to improve their patient selection for PHI.

It is remarkable that for the most part, PHI is appropriately used, especially in low-use areas. Based on the prevailing concern for the safety of PHI due to difficulty with maintenance of intubation skills in low-PHI use prehospital systems, it is somewhat surprising to find that areas of limited PHI use actually confer less risk to trauma patients due to PHI. One potential explanation may be that in low-use regions, the number of prehospital providers trained to perform intubation is also low and hence these medics may accumulate intubating experience at a higher rate than those in high-use regions, making them more efficient with the intubation procedure [55]. In fact, Table 5 reveals that the proportion of patients in the overall population of trauma patients that gets harmed by PHI is higher in high-use regions (20%) than in low-use regions (13.5%), although the difference did not reach statistical significance. We believe that patient case-mix is uniformly distributed over these regions (hence use of regional variations as an IV in the first place with necessary tests provided to this end) and does not contribute towards these discrepancies. It is possible that the skill level of the intubating provider, and therefore, the quality of the PHI procedure in itself is different across the regions. Interestingly, in the LIV context, this does not invalidate the IV, as only regions with close but different levels of use are used to estimate local effects. The estimated average effects from the LIV methods therefore may capture the plausible gradation in the quality of PHI were its use extended to the entire population.

Additionally, the difference in the level of PHI risk among PHI recipients between low and high-PHI regions may be explained by patient selection for PHI. Our analysis also reveals that those patients without head injury, with lower injury severity and without prehospital shock had a higher likelihood of significant harm from PHI. Not surprisingly, areas with high rates of PHI use had a lower risk reduction due to positive self-selection, presumably because the indications for PHI were liberalized. Ultimately, the positive effects of PHI are more pronounced when it is reserved for only the most critically ill patients that survive to the emergency department, and

when the indication for PHI is expanded beyond this, the risk of PHI outweighs the risk of mortality without PHI. Furthermore, those patients transported from the field to non-trauma centers after PHI were more likely to be harmed by PHI. It is not clear whether this is a result of the care subsequently delivered at the non-trauma hospital, or the combined patient and system factors that would lead prehospital providers to perform PHI and transport to a non-trauma hospital.

One limitation of our study is that the prehospital death rate is unknown; patients who were declared dead at the scene, en route, or within 30 minutes of arrival if they arrived at the hospital without signs of life were excluded from the NSCOT study. If PHI has a differential effect on pre-hospital mortality than no PHI, then focusing analysis on patients who reach the hospital may provide biased assessment of PHI. It should also make the case mix of patients who reach the hospital alive in low-use regions different from that in high-use regions, thereby invalidating the IV. However, we did not find any evidence of such differential case-mix in our observed data. Moreover, we believe that even if there may be a differential effect of PHI on pre-hospital mortality, it is likely to be quite small as the overall rate of pre-hospital mortality in patients with severe trauma is small (~3% [56]).

Overall, we believe that the methods highlighted in this paper can provide a rich set of tools for researchers to explore hypothesis on heterogeneity in treatment effects. Obviously, it is necessary to replicate these results before they are implemented in practice. However, such results can provide informative priors for designing confirmatory trials/studies in this setting, thereby making the link between information generation and decision making more efficient, and in line with accomplishing the goals of CER.

## Appendix:

$$\begin{aligned}
E(Y | Z = z, X = x) &= E(DY_1 + (1 - D)Y_0 | Z = z, X = x) \\
&= E(Y_0 | X = x) + E(D(Y_1 - Y_0) | Z = z, X = x) \\
&= E(Y_0 | X = x) + \Pr(D = 1 | Z = z, X = x) \cdot E((Y_1 - Y_0) | D = 1, X = x) \\
&= E(Y_0 | X = x) + \Pr(D = 1 | Z = z, X = x) \cdot \frac{\int_0^1 E((Y_1 - Y_0) | U_D = u, X = x) du}{\int_0^1 du} \\
&= E(Y_0 | X = x) + \Pr(D = 1 | Z = z, X = x) \cdot \int_{S(z,x)=1-P(z,x)}^1 E((Y_1 - Y_0) | U_D = u, X = x) du,
\end{aligned}$$

where the last equality follows as  $D = (U_D > S(z, x))$  and therefore,

$$\Pr(D = 1 | Z = z, X = x) = \int_{S(z,x)=1-P(z,x)}^1 du.$$

Now, if we take the rate of change of the mean outcome with respect to the probability of receiving treatment evaluated at a particular value of  $S(z, x) = 1 - P(z, x)$ :

$$\frac{\partial}{\partial P(z, x)} E(Y | Z = z, X = x) \bigg|_{1 - P(z, x) = u_D} = E((Y_1 - Y_0) | X = x, u_D = 1 - P(z, x)) = \text{MTE}(x, u_D)$$

The formal proof of consistency for this estimator can be found in Heckman et al. (2006).

Figure 1: A stylized illustration of non-essential (a & b) and essential heterogeneity (c) and estimation of marginal treatment effect (MTEs) using the local instrumental variable (LIV) approach (d).

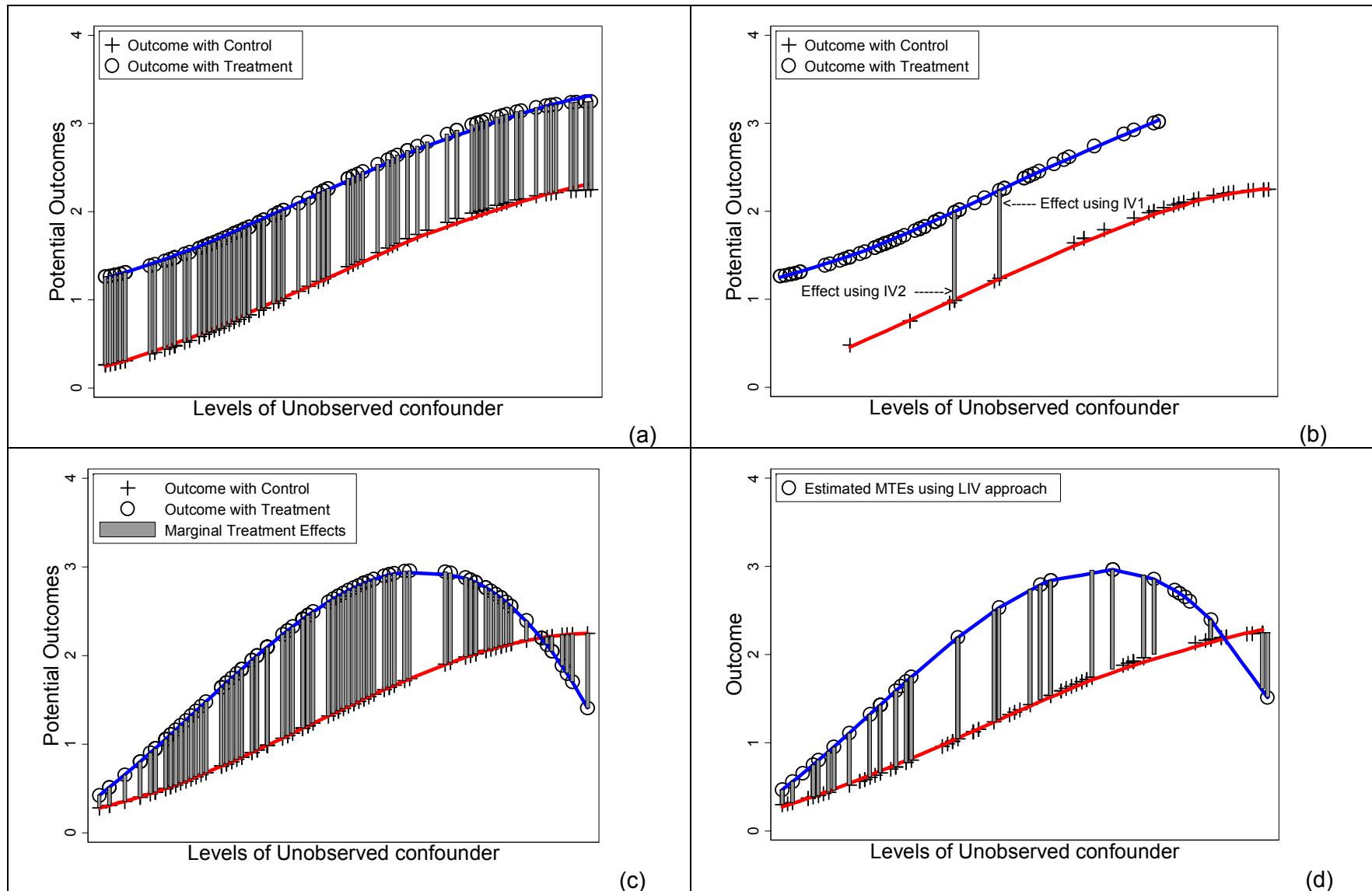


Figure 2: Distribution of estimated propensity score to receive prehospital intubation for receivers and non-receivers of prehospital intubation, conditional on observed confounders and instrumental variables.

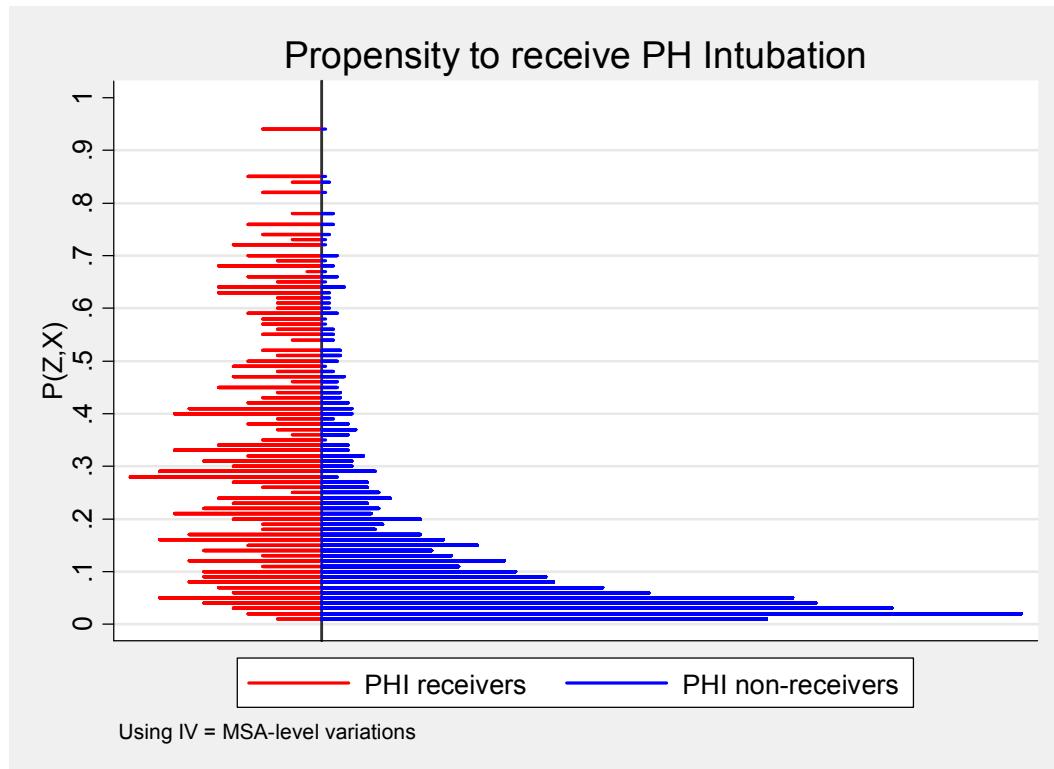


Figure 3: (a): Marginal treatment effect profile with 95% confidence band (averaged over observed confounders) across the propensity to receive prehospital intubation based on unobserved confounders ( $U_D$ ). (b) Average treatment effect profile and its 95% confidence band across deciles of linear predictor from the LIV estimand (eq 3). (Black dots indicate that treatment effects that are significantly different that zero.)

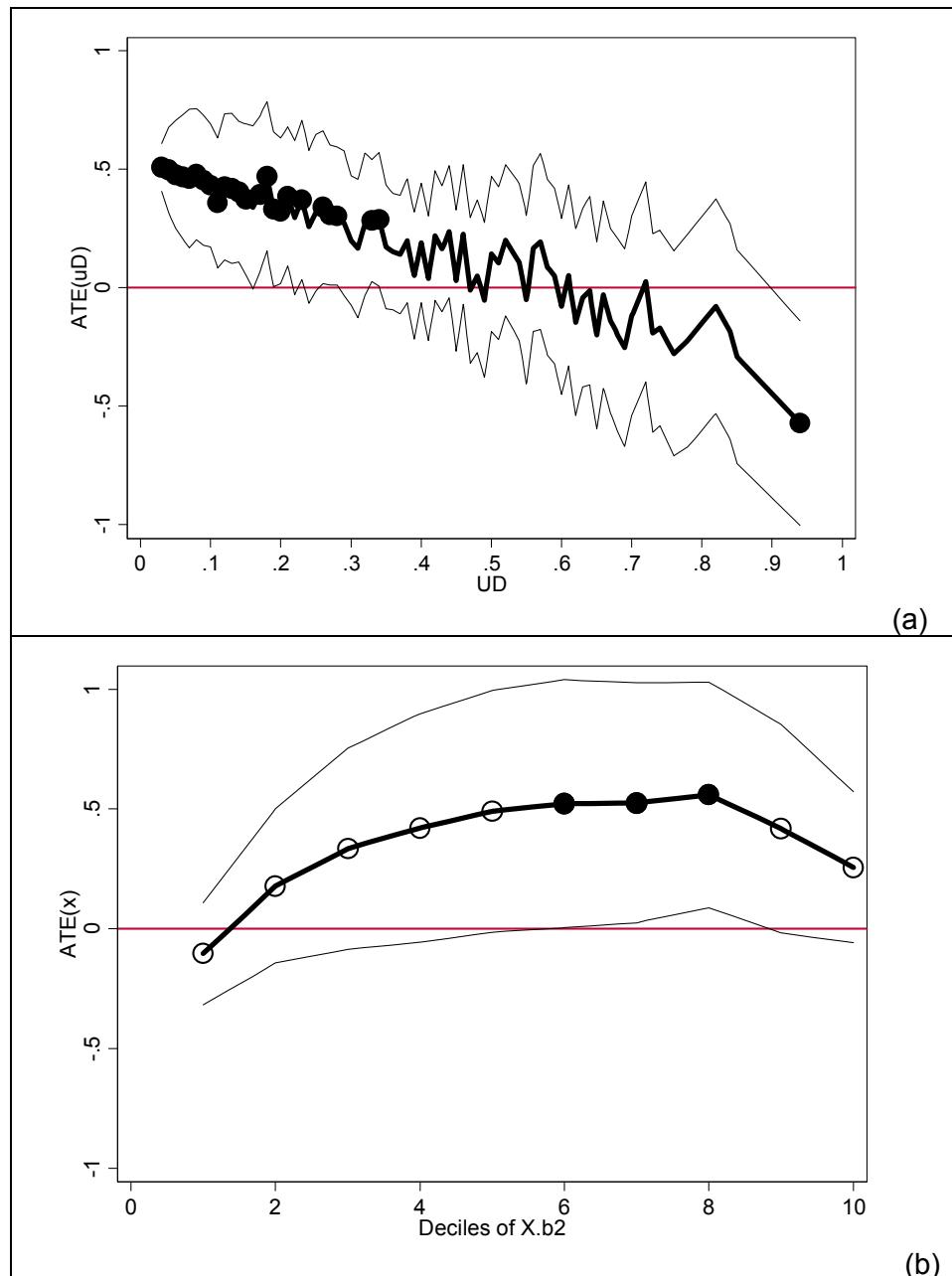


Table 1: Characteristics of observed confounders across treatment arms

Characteristics	No Prehospital Intubation N = 1655	Prehospital Intubation N = 514	p-value	p-value across IV levels*
	% or Mean (sd)	% or Mean (sd)		
Age (in years)	39 (18)	47 (20)	< 0.001	0.44
Age 18 – 24	22.9%	33.0%		
Age 25 - 34	17.6%	24.1%		
Age 35 – 44	18.9%	14.1%		
Age 45 – 54	15.2%	13.1%		
Age 55 – 64	9.9%	9.1%		
Age > 64	26.1%	12.3%	< 0.001	0.26
Female	26.4%	29.1%	0.27	0.25
Race/Ethnicity:				
Hispanic	20.8%	14.7%		
Non Hispanic White	49.3%	67.8%		
Non Hispanic Black	29.9%	17.5%	0.07	0.09
Pre-injury Insurance:				
Uninsured	32.5%	29.9%		
Medicare	17.7%	8.9%		
Private only	38.3%	41.5%		
Medicaid and Other	11.5%	19.7%	0.02	0.02
Prehospital shock	13.1%	27.2%	<0.001	0.70
Severe head injury	49.3%	76.3%	<0.001	0.10
Admitted to a Trauma Center	86%	88%	0.12	0.64
Charlson comorbidity				
No comorbidity	74.0%	86.1%		
1 comorbidity	14.6%	5.7%		
2 comorbidities	5.2%	4.5%		
3+ comorbidities	6.3%	3.7%	0.002	0.05
ISS Score quartiles:				
16-24	57.1%	28.6%		
25-34	33.9%	39.4%		
>34	9.0%	32.0%	< 0.001	0.81
In-hospital death	24%	65%	< 0.001	< 0.001

\* Comparison of covariate levels between above and below median values of the IV. ISS=Injury Severity Score.

Table 2: Treatment effect estimates of prehospital intubation compared to no prehospital intubation on inpatient mortality, across alternative methods.

Estimator	Mean effect (se) [p-value]
Unadjusted	<b>0.410 (0.02) [&lt;0.001]</b>
Regression (Logistic)	<b>0.188 (0.04) [&lt;0.001]</b>
IV (2stage residual inclusion)	0.029 (0.09) [0.45]
LIV-based estimates	
IV-effect	0.047 (0.09) [0.60]
Average Treatment Effect	<b>0.322 (0.16) [0.04]</b>
Effect on the Treated	0.046 (0.07) [0.61]

Table 3: Logistic regression exploring association of observed confounders with likelihood of significant harm versus non-significant effect (reference) from undergoing PHI versus no-PHI. Reference categories: For age was age > 64 years; for comorbidities was  $\geq 3$  comorbidities; for race was Non Hispanic Black; for insurance was Medicaid or other; for ISS categories was ISS>34.

Signf.+ve MTE	Odds Ratio	Robust Std. Err.	z	P> z	[95% Conf. Interval]
Age 18-24	.3610035	.2287032	-1.61	0.108	.1042936 1.249584
Age 25-34	.4645746	.2543745	-1.40	0.161	.1588496 1.358704
<b>Age 35-44</b>	<b>.1987791</b>	<b>.1104993</b>	<b>-2.91</b>	<b>0.004</b>	<b>.0668646</b> <b>.5909426</b>
Age 45-54	1.459425	.8036378	0.69	0.492	.4959807 4.294366
<b>Age 55-64</b>	<b>.1426938</b>	<b>.0921639</b>	<b>-3.01</b>	<b>0.003</b>	<b>.040237</b> <b>.5060393</b>
No comorb.	4.007541	2.834283	1.96	0.050	1.00202 16.02801
<b>1 comorb.</b>	<b>6.832509</b>	<b>3.379375</b>	<b>3.89</b>	<b>0.000</b>	<b>2.591636</b> <b>18.01302</b>
2 comorb.	4.088569	2.987609	1.93	0.054	.976291 17.12235
<b>Female</b>	<b>.566381</b>	<b>.1188147</b>	<b>-2.71</b>	<b>0.007</b>	<b>.3754436</b> <b>.8544226</b>
<b>Hispanic</b>	<b>.1621984</b>	<b>.0760913</b>	<b>-3.88</b>	<b>0.000</b>	<b>.0646736</b> <b>.4067863</b>
<b>Non H White</b>	<b>.5394264</b>	<b>.1418702</b>	<b>-2.35</b>	<b>0.019</b>	<b>.3221547</b> <b>.9032333</b>
No insurance	.4903473	.1917467	-1.82	0.068	.2278492 1.055261
<b>Medicare</b>	<b>.0857763</b>	<b>.0467833</b>	<b>-4.50</b>	<b>0.000</b>	<b>.0294519</b> <b>.2498169</b>
<b>Private only</b>	<b>.093989</b>	<b>.0419582</b>	<b>-5.30</b>	<b>0.000</b>	<b>.0391821</b> <b>.2254585</b>
<b>PH shock</b>	<b>.1840843</b>	<b>.0470659</b>	<b>-6.62</b>	<b>0.000</b>	<b>.1115283</b> <b>.3038423</b>
<b>Head Injury</b>	<b>.4435504</b>	<b>.1158232</b>	<b>-3.11</b>	<b>0.002</b>	<b>.2658709</b> <b>.7399716</b>
<b>Trauma Centr</b>	<b>.1748241</b>	<b>.0663716</b>	<b>-4.59</b>	<b>0.000</b>	<b>.08307</b> <b>.3679242</b>
<b>ISS 16-24</b>	<b>12.29417</b>	<b>5.26669</b>	<b>5.86</b>	<b>0.000</b>	<b>5.309503</b> <b>28.4672</b>
<b>ISS 25-34</b>	<b>17.39305</b>	<b>8.891313</b>	<b>5.59</b>	<b>0.000</b>	<b>6.386199</b> <b>47.37064</b>

Bold face indicates p-value < 0.05

Table 4: Logistic regression exploring association of observed confounders with likelihood of significant harm versus non-significant effect (reference) from undergoing PHI versus no-PHI among those who receive PHI. Reference categories: For age was age > 64 years; for comorbidities was  $\geq 3$  comorbidities; for race was Non Hispanic Black; for insurance was Medicaid or other; for ISS categories was ISS>34.

teff	Odds Ratio	Robust				[95% Conf. Interval]
		Std. Err.	z	P> z		
Age 18-24	.0840663	.1572976	-1.32	0.186	.0021475	3.290921
Age 25-34	.2078945	.4113418	-0.79	0.427	.0043018	10.04703
Age 35-44	.0403868	.0723614	-1.79	0.073	.0012054	1.353147
Age 45-54	1.978708	4.000658	0.34	0.736	.0376163	104.0847
Age 55-64	.1895042	.3502777	-0.90	0.368	.0050614	7.095309
No comorb.	.2468598	.4076757	-0.85	0.397	.0096992	6.282958
1 comorb.	.1506004	.2345979	-1.22	0.224	.0071099	3.189967
2 comorb.	.1353582	.2621266	-1.03	0.302	.0030416	6.023808
Female	.5384088	.2199448	-1.52	0.130	.2417624	1.199045
<b>Hispanic</b>	<b>.1245016</b>	<b>.0654659</b>	<b>-3.96</b>	<b>0.000</b>	<b>.0444215</b>	<b>.3489447</b>
<b>Non H White</b>	<b>.1183554</b>	<b>.0578364</b>	<b>-4.37</b>	<b>0.000</b>	<b>.0454186</b>	<b>.3084198</b>
<b>No insurance</b>	<b>.1273144</b>	<b>.0692645</b>	<b>-3.79</b>	<b>0.000</b>	<b>.0438316</b>	<b>.3698006</b>
Medicare	.0636736	.1151043	-1.52	0.128	.0018417	2.20139
<b>Private only</b>	<b>.0456413</b>	<b>.0283607</b>	<b>-4.97</b>	<b>0.000</b>	<b>.0135032</b>	<b>.1542691</b>
<b>PH shock</b>	<b>.1452067</b>	<b>.0805782</b>	<b>-3.48</b>	<b>0.001</b>	<b>.048937</b>	<b>.4308597</b>
<b>Head Injury</b>	<b>.1622299</b>	<b>.0733337</b>	<b>-4.02</b>	<b>0.000</b>	<b>.0668894</b>	<b>.3934635</b>
<b>Trauma Centr</b>	<b>.1324008</b>	<b>.0642135</b>	<b>-4.17</b>	<b>0.000</b>	<b>.0511757</b>	<b>.3425448</b>
<b>ISS 16-24</b>	<b>16.27762</b>	<b>12.58291</b>	<b>3.61</b>	<b>0.000</b>	<b>3.577635</b>	<b>74.06036</b>
<b>ISS 25-34</b>	<b>21.00515</b>	<b>16.24184</b>	<b>3.94</b>	<b>0.000</b>	<b>4.61477</b>	<b>95.60963</b>

Bold face indicates p-value < 0.05

Table 5: Comparing low PHI use regions to high PHI use regions for degree of positive self-selection of PHI use.

Proportion who would get harmed by PHI [p-value]	Low PHI use regions (< Median rate)	High PHI-use regions ( $\geq$ Median rate)	p-value for Difference
Among all patients	13.5% [<0.001]	20.7% [<0.001]	0.10
Among patient receiving PHI	7.2% [<0.001]	16.2% [<0.001]	0.02
Risk reduction due to positive self-selection	-47% [0.02]	-22% [0.07]	0.003

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