Introduction: Significant heterogeneity exists in traumatic brain injury (TBI) outcomes. In the United States, TBI remains a primary driver of injury-related mortality and morbidity. Prior work has suggested that disparity exists in rural areas; our objective was to evaluate potential differences in TBI mortality across urban and rural areas on a national scale. Methods: Age-adjusted TBI fatality rates were obtained at the county level across the U.S. from 2008 to 2014. To evaluate geography, urban influence codes (UIC) were also obtained at the county level. Metropolitan counties are defined as those with an UIC ≤2, while nonmetropolitan counties are defined as an UIC ≥3. County-level fatality rates and UIC classification were geospatially mapped. Linear regression was used to evaluate the change in TBI fatality rate at each category of UIC. The median TBI fatality rate was also compared between metropolitan and nonmetropolitan counties. Results: Geospatial analysis demonstrated higher fatality rates distributed among nonmetropolitan counties across the United States. The TBI fatality rate was 13.00 deaths per 100,000 persons higher in the most rural UIC category compared to the most urban UIC category (95% confidence interval 12.15, 13.86; \( P < 0.001 \)). The median TBI rate for nonmetropolitan counties was significantly higher than metropolitan counties (22.32 vs. 18.22 deaths per 100,000 persons, \( P < 0.001 \)). Conclusions: TBI fatality rates are higher in rural areas of the United States. Additional studies to evaluate the mechanisms and solutions to this disparity are warranted and may have implications for lower- and middle-income countries. Keywords: Disparity, geographic, lower-middle-income countries, rural, traumatic brain injury.
treatments and outcomes. However, it is not known whether treatments and outcomes for patients with TBI differ between rural and urban environments on a national scale. The primary objective of this study was to evaluate the relationship between TBI mortality and rural geography across the United States. We hypothesized that TBI mortality would be higher in rural areas of the United States than in urban areas.

**Methods**

**Data sources**

The Centers for Disease Control Web-based Injury Statistics Query and Reporting System was queried to identify the age-adjusted TBI-specific fatality rate per 100,000 population from 2008 to 2014 for the United States at the county level. TBI was defined based on the International Classification of Disease, 10th Revision (ICD-10) codes. These codes represent patient-level diagnoses of specific injuries. The codes used for this study represent concussion or internal head injuries including the following codes: S01.0–S01.9, S02.0, S02.1, S02.3, S02.7–S02.9, S04.0, S06.0–S06.9, S07.0, S07.1, S07.8, S07.9, S09.7–S09.9, T90.1, T90.2, T90.4, T90.5, T90.8, and T90.9. Age adjustment was performed using the direct method across 5-year age categories against the standard United States population in the year 2000. These rates were also geospatially smoothed to account for areas with fewer than 20 deaths over the period. This method calculates the rate for the counties with fewer than 20 deaths, using the county deaths and deaths in counties that border it, and to develop a local neighborhood rate for the small geographic locale of typically six–eight counties.

County-level urban influence codes (UIC) as developed by the U.S. Department of Agriculture were then merged with U.S. counties. The UIC scale ranges from 1 to 12, with one representing the most urban counties with a metro area of 1+ million residents, and 12 representing the most rural counties without a town of at least 2500 residents. The UIC is based on both geographic adjacencies to large metro areas as well as the percent of population in a county that commutes to metro areas. Metropolitan counties are defined as those with a UIC ≤2, while nonmetropolitan counties are defined as those with a UIC ≥3.

**Geospatial analysis**

County-level TBI fatality rates were mapped across the United States [Figure 1], represented by color ramp (high values red; low values tan), to evaluate the specific geographic pattern of TBI fatalities and geographic location in the country. In addition, a patterned overlay was added to indicate whether the county is classified as metropolitan or nonmetropolitan based on the UIC as described above to allow visual inspection of TBI fatality rates and rurality across the U.S. [Figure 2]. All geospatial analyses were performed using ArcGIS v10.5 (ESRI, Redlands, CA).

**Statistical analysis**

The mean TBI fatality rate was calculated within each UIC category and plotted over UIC to evaluate the relationship between TBI fatality rate and incrementally
more rural areas in the United States. Linear regression was used to evaluate the change in TBI fatality rate at each category of UIC with the most urban UIC category as the reference. Regression coefficients for the most rural UIC category compared to the most urban UIC category are presented below. The median TBI fatality rate was also compared between metropolitan versus nonmetropolitan counties (defined above) by UIC, using the Wilcoxon rank-sum test. These evaluations were stratified by all TBI deaths, unintentional TBI deaths, and TBI deaths as a result of violence. The intention of TBI deaths was determined using the ICD-10 external cause of injury code matrix. Data analysis was conducted using Stata v15 (StataCorp; College Station, TX, USA).

**RESULTS**

It was observed that higher fatality rates were distributed among mid-Western and Southern counties, representing more rural areas of the United States (dark red) [Figure 1]. Applying the metropolitan/nonmetropolitan overlay (black pattern) also demonstrated higher fatality rates distributed among nonmetropolitan counties across the U.S. [Figure 2].

There was a direct relationship between mean TBI fatality rates and UIC demonstrating higher TBI fatality rates across all intentions for more rural counties [Figure 3]. For all TBI, the fatality rate was 13.00 deaths per 100,000 persons higher in the most rural UIC category compared to the most urban UIC category (95% confidence interval [CI] 12.15, 13.86; \( P < 0.001 \)). The TBI fatality rate was 9.34 deaths per 100,000 persons (95% CI 8.75, 9.93; \( P < 0.001 \)) higher in the most rural category for unintentional injury and 4.61 deaths per 100,000 persons (95% CI 4.12, 5.11; \( P < 0.001 \)) higher in the most rural category for violent injury. The median TBI fatality rate was also significantly higher in nonmetropolitan counties compared to metropolitan counties [Figure 4]. The median TBI fatality rate from all causes was 23% higher in rural relative to urban America (\( P < 0.001 \)), while the median TBI fatality rate was 30% higher from unintentional injury and 16% higher from violent injury in rural relative to urban American areas (\( P < 0.001 \), respectively).

**DISCUSSION**

TBI is a critical global public health concern that is both widespread and costly: an estimated 69 million new cases occur annually, at a global cost of $400 billion USD.\(^{[16,17]}\) The incidence of TBI is rising, with disproportionate increases in lower- and middle-income countries (LMICs).\(^{[16]}\) The World Health Organization estimates that it will become the third major cause of death and disability by 2020.\(^{[18]}\)

Even, within the United States, a high-income country (HIC), TBI remains a significant cause of morbidity and mortality. In 2010, an estimated 2.5 million TBI-related emergency department visits, hospitalizations, and deaths occurred in the U.S., and one-third of all injury-related deaths were TBI-related; these figures are believed to
An estimated 4.6 million cases occur annually in the U.S. and Canada, and up to 5.3 million people in the U.S. live with the sequelae of TBI.\textsuperscript{[16,19]} For Americans, TBI carries an estimated lifetime cost of $396,000 per person.\textsuperscript{[20]}

This study contributes important information to the growing body of evidence that patients, who sustain TBI in rural, predominantly low-resource environments have a significantly higher risk of death than those in urban, high-resource environments. This finding has been demonstrated in previous work by comparing outcomes from TBI in LMICs and HICs.\textsuperscript{[9,21,22]} In this study, within the HIC of the United States, the disparity in outcomes from TBI for patients in rural versus urban environments is clearly demonstrated; all-cause mortality from TBI is 23% higher in rural areas relative to urban areas of the United States.

Guidelines for the management of TBI have been shown to reduce the burden of mortality and morbidity in mature, resource-rich environments.\textsuperscript{[6,23,24]} Multiple studies have found that adherence to the most widely adopted guidelines for TBI management, developed by the Brain Trauma Foundation, has helped to reduce TBI-related mortality.\textsuperscript{[25,26]} These evidence-based guidelines have now been available for the past 20 years.\textsuperscript{[27-29]} However, their clinical application remains limited for two major reasons.

First, the treatment recommendations can only be generated where evidence is available. The recent update of the Guidelines for the Management of Severe TBI provides 28 recommendations as follows: one Level I, 18 Level II, and nine Level III.\textsuperscript{[29]} These recommendations provide some information that can be used for a “bedside” clinical protocol, but major gaps remain; to create a complete clinical protocol, it is necessary to fill those gaps using consensus from clinical experts.\textsuperscript{[30]}

Second, the guidelines are mainly derived from studies conducted in HICs, and as such are specific to high-resource environments. They have limited applicability in resource-poor settings, a common scenario in LMICs.\textsuperscript{[1,17]} LMICs and rural populations within the U.S. also have unique epidemiological characteristics and capacity-building constraints that limit the optimal implementation of existing TBI guidelines.\textsuperscript{[31]} Most guidelines do not address costs and barriers to implementation or epidemiologic factors that may influence the outcome.\textsuperscript{[1,32,33]} As such, recent efforts to implement well-validated, guideline-recommended interventions in LMICs have yielded mixed results.\textsuperscript{[1,34]} As the recognition of these limitations has grown, multiple efforts have been undertaken to develop evidence-based practices for low-resource environments. Till date, many of these efforts are country-specific or region-specific, for example, Sub-Saharan Africa, Hungary, and Colombia.\textsuperscript{[35-37]}

There is evidence that even within the United States, unequal distribution of healthcare facilities and resources exists.\textsuperscript{[15,25,26,38]} Similarly, adoption of evidence-based guidelines for TBI is not uniform across the U.S., with resource-limited, rural areas demonstrating lower levels of adherence than their comparatively wealthier urban counterparts.\textsuperscript{[8,9,26]}

Taken together, the lack of evidence for complete clinical protocols and the lack of evidence specific to low-resource environments render currently available evidence-based guidelines of questionable generalizability in both LMICs and rural areas of HICs.
For the most part, efforts to implement and assess clinical protocols that are specific to low-resource environments have taken place in LMICs. The feasibility of conducting such a study in a HIC, however, is limited. For example, although 60 million people live in rural areas of the U.S., the number of patients per center presenting with severe TBI is low. To collect a meaningful sample size in the U.S., it would be necessary to recruit many centers in many regions of the country and collect data over an extended period. The costs of such a multicenter study would be prohibitively high and the logistical and organizational challenges expansive. A low-resource environment with a high percent census of severe TBI patients would allow for a more efficient and less costly means of collecting data that can address which interventions are most effective in improving outcomes from severe TBI in low-resource environments.

Granted, differences exist between LMICs and rural areas of HICs regarding characteristics such as demographics, epidemiological factors, prevailing injury patterns, and availability of treatment resources – These differences may limit the generalizability of findings from populations in an LMIC to populations in rural areas of HICs. Nevertheless, a well-controlled study in an LMIC with a sample size sufficient to utilize robust and flexible analytic methods may provide information that would be useful to rural regions of HICs.

**Conclusions**

TBI fatality rates are higher in rural areas of the United States relative to urban areas. This disparity is likely due in part to differences in resource availability. Additional studies are needed to (1) better characterize the unmet needs of rural Americans who sustain TBI and (2) develop treatment guidelines that can effectively address the unique conditions and resource limitations contributing to poorer outcomes from TBI in these communities. Similarly, investigations done in resource-constrained LMICs may have important implications for improving outcomes from TBI in rural areas of HICs.

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**Conflicts of interest**

There are no conflicts of interest.

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