Relative Mortality Analysis of the "golden hour": A comprehensive acuity stratification approach to address disagreement in current literature

Philip H. Schroeder[a], Nicholas J. Napoli[a], PhD, MS, William F. Barnhardt[b], Madeline E. Kotoriy[c], MPP, and Jeffrey S. Young[d], MD, MBA

[a]Department of Systems and Information Engineering, University of Virginia, Charlottesville, VA, USA; [b]Emergency Services, University of Virginia Health System, Charlottesville, VA, USA; [c]Batten School of Leadership & Public Policy, University of Virginia, Charlottesville, VA, USA; [d]Department of Surgery, University of Virginia Health System, Charlottesville, VA, USA

ABSTRACT

Study Objective

This study sought to address the disagreement in literature regarding the "golden hour" in trauma by using the Relative Mortality Analysis (RMA) to overcome previous studies' limitations in accounting for acuity when evaluating the impact of pre-hospital time (PHT) on mortality.

Methods

The methods of previous studies that failed to support the "golden hour" were compared to the RMA on how they capture the relationship between PHT and mortality in the University of Virginia Trauma Center population. Unlike previous studies that rely on an acuity threshold based on univariate metrics to account for acuity in their populations, the RMA stratifies patients based on acuity using the comprehensive triage metric of probability of survival (PoS), calculated with Trauma and Injury Severity Score methodology, to evaluate the impact of PHT across the full spectrum of acuity.

Results

Previous studies' methods all failed to identify patients who benefited from reduced PHT, just as they did in the original studies. However, the RMA identified a subgroup, 9.9% (with PoS 23% - 91%), of the 5,063 patient population with significantly lower mortality when transported to the hospital within one hour, supporting the "golden hour."

Conclusion

These results suggest that previous studies' limitations in accounting for acuity have contributed to the disagreement in "golden hour" literature by precluding identification of patients who benefited from reduced PHT within their populations. The RMA overcomes these limitations and demonstrated that the "golden hour" is significant for patients who are not low acuity (PoS > 91%) or severely high acuity (PoS < 23%).

INTRODUCTION

Background

The "golden hour" of trauma refers to the principle that the sooner a patient receives definitive hospital care following an injury, the greater their chance of survival. However, extensive literature reviews have found conflicting evidence regarding the validity of this premise.[1,2] Of studies that found a positive correlation between pre-hospital time (PHT) and mortality,[3-12] most evaluated either a small sample of patients suffering spe- cific injuries[3-8] or a mixed sample that included nontraumatic cardiac arrest.[9,10] Of studies that evaluated an inclusive sample of solely trauma patients,[11-19] seven directly evaluated the relationship between PHT and outcome.[11,12,15-19] Of these, two provided support for the "golden hour"[11,12] while five failed to identify any patients who benefited from reduced PHT.[15-19]

Importance

Disagreement in literature regarding the "golden hour" may stem from limitations in previous studies' attempts to account for the confounding effects of patient acuity on the relationship between PHT and mortality. Previous studies have attempted to account for acuity by using univariate metrics, such as Injury Severity Score (ISS) or Glasgow Coma Scale (GCS), to establish an acuity threshold for their study populations,[16-19] which limit their ability to fully capture the multisystem nature of trauma injuries.[20] For example, a 54 year-old blunt trauma patient with an ISS of 20 can have a Trauma and Injury Severity Score (TRISS) calculated probability of survival (PoS) that ranges from 7% - 99%.[21] Further, no study has assessed the impact of PHT on mortality among different patient acuity levels. This analysis addresses these gaps by employing a novel patient stratification approach that analyzes the impact of PHT on mortality across different levels of patient acuity, using the comprehensive triage metric of PoS.[21] Ultimately, insights from this analysis will address the disagreement in "golden hour" literature and better inform Emergency Medical Services (EMS), which currently commit significant resources (e.g., emergency vehicles, staffing, training) and undertake dangerous risks (e.g., aeromedical evacuation, hasty extrication, assessment, treatment, and transport) to reduce PHT for trauma patients.[23-29]

Goals of This Investigation

This study sought to address the disagreement in literature regarding the "golden hour" by using a more comprehensive approach of accounting for patient acuity than that used in previous studies. To do so, this study evaluated the "golden hour" using the Relative Mortality Analysis (RMA), which stratifies patients based on acuity using TRISS calculated PoS. TRISS methodology integrates both physiological measures, with Revised Trauma Score, and anatomical measures, with ISS, to provide for a comprehensive calculation of patient acuity, represented as PoS.[21] Methods of the previous studies that failed to support the "golden hour" were

Philip H. Schroeder, phs5eg@virginia.edu, Systems and Information Engineering, University of Virginia, 151 Engineer's Way, Charlottesville, VA 22904, USA.

compared to the RMA on how they capture the relationship between PHT and mortality. Unlike the approaches of these previous studies, the RMA uses a comprehensive triage metric and evaluates the impact of PHT across the full spectrum of patient acuity. By using the RMA, this study sought to demonstrate how acuity affects the impact of PHT on mortality and, ultimately, how previous studies' limitations in accounting for acuity may have caused the current disagreement in "golden hour" literature.

METHODS

Study Setting

This secondary analysis was conducted with the approval of the University of Virginia (UVA) Institutional Review Board for Health Sciences Research. All statistical analysis was performed using Matlab®, 2016 (Mathworks, Natick, MA). The collected data was provided by the trauma registry of the UVA Health System, an American College of Surgeons Verified Level I trauma center. The database encompasses 20,217 patient encounters from 1993 to 2015.

Selection of Participants

Only patients with a recorded Glasgow Coma Scale (GCS), respiratory rate (RR), systolic blood pressure (SBP), injury type (blunt or penetrating), injury time, injury date, Emergency Department (ED) arrival time, and ED arrival date were included. Consistent with previous studies, the analysis included only patients transported to the trauma center by a pre-hospital care team from the incident scene within 120 minutes of the injury time. Patients with complete data were compared to patients with incomplete data using a two-sample t-test for continuous variables and a chi-square test of independence for categorical variables.

Relative Mortality Analysis

The RMA employed two tools, the Relative Mortality Metric (RMM) and the Relative Mortality Performance Trend (RMPT), to evaluate the impact of PHT on mortality across the full spectrum of patient acuity within the UVA Trauma Center population. As stated, patient acuity was quantified using TRISS calculated PoS. [20, 21]

The patient population was divided into bins based on PoS intervals. Patients in each bin were then divided into two cohorts based on their PHT, calculated as the difference between injury time and ED arrival time. Guided by the "golden hour" principle of trauma, the short PHT cohort represented patients with a PHT within 0 and 60 minutes ($0 \leq PHT \leq 60$) and the long PHT cohort represented patients with a PHT between 60 and 120 minutes ($60 < PHT \leq 120$). The observed mortality (O_b) for the long PHT and short PHT cohorts of each bin represented the proportion of patients who died (D_b) among the total number (N_b) of patients within the given cohort,

$$O_b = \frac{Db}{Nb}.$$

Using normal approximation, the error (E_b) for the O_b value was calculated by,

$$E_b = Z\sqrt{\frac{Ab(1-Ab)}{Nb}},$$

where A_b (calculated as $A_b = 1 - PoS$) represented the anticipated mortality for each cohort and $Z = 1.96$ to ensure 95% confidence.

From this, the minimum number of patients required to achieve a specific E_b was calculated as,

$$N_b = \frac{Z^2(Ab(1-Ab))}{Eb^2}.$$

The PoS ranges for the bins are nonlinear and can be dynamically adjusted to achieve the optimal balance of resolution and statistical power (i.e., smaller PoS ranges, comprised of less patients, provide greater resolution among the patient acuity levels, while larger PoS ranges, comprised of more patients, provide greater statistical significance in the calculations of observed mortality). To achieve the greatest degree of resolution among the higher acuity population, the PoS ranges for bins representing patients with a PoS < 91% were sized to ensure the smallest cohort, either the long PHT or short PHT cohort, within the bin included only the minimum number of patients (N_b) needed to maintain an error of less than 0.08 ($E_b < 0.08$) for the calculation of the cohort's O_b.

Each bin's O_b is plotted, with each bin represented by the median PoS value of the bin's PoS range. A population's RMPT refers to the trend that results when plotting each cohort's O_b with respect to each bin's median PoS value. The anticipated mortality is plotted along with the RMPT. The RMM is a value representing the area between the anticipated mortality line and the RMPT for the populations. The RMM for each cohort was calculated by,

$$RMM = 1 - \frac{\sum_{b=1}^{j} Rb\ Ob}{\sum_{b=1}^{j} Rb\ Ab},$$

where R_b represented the PoS range for each bin. The lower limit (RMM_{LL}) and upper limit (RMM_{UL}) of the RMM were calculated by,

$$RMM_{LL} = 1 - \frac{\sum_{b=1}^{j} Rb\ (Ob+Eb)}{\sum_{b=1}^{j} Rb\ Ab}$$

$$RMM_{UL} = 1 - \frac{\sum_{b=1}^{j} Rb\ (Ob-Eb)}{\sum_{b=1}^{j} Rb\ Ab}.$$

The RMM ranges from -1 to +1, where a positive value is indicative of an RMPT below the anticipated mortality line (i.e., observed mortality is below anticipated mortality) and vice versa. Together, the RMPT and RMM provided both a graphical and numerical illustration of mortality across the full spectrum of patient acuity in both the short PHT and long PHT cohorts.

Methods of Previous Studies

Methods of the previous studies that failed to support the "golden hour" were compared to the RMA on how they capture the relationship between PHT and mortality. These studies included those of Lerner et al.,[15] Kleber et al.,[16] Petri et al.,[17] Di Bartolomeo et al.,[18] and Newgard et al.[19] Of these studies, Kleber et al., Petri et al., Di Bartolomeo et al., and Newgard et al. each attempted to account for patient acuity by using univariate metrics to establish an acuity threshold for their study population, with the goal of establishing a study population of only patients who are high acuity and, thus, thought to be the most sensitive to PHT.[15-19] Application of these four studies' acuity thresholds produced four different study populations. Lerner et al. did not use an acuity threshold or make any attempt to account for acuity in their patient population.[15] Thus, the study population representing Lerner

Philip H. Schroeder, phs5eg@virginia.edu, Systems and Information Engineering, University of Virginia, 151 Engineer's Way, Charlottesville, VA 22904, USA.

et al. in this study was the same as that used with the RMA (i.e., the entire UVA Trauma Center population).

Each of the five study populations, created by the five different population selection methods, were assessed to determine the extent to which patient mortality was impacted by PHT. To maintain consistency and allow for direct comparison between the five previous studies and this study, the assessment of each study population was conducted using the primary analysis methods among the five previous studies: multivariable logistic regression,[15,16,18,19] comparison of mean PHT between survivors and nonsurvivors,[15,17] and plotting survival across increasing intervals of PHT.[16,18]

The multivariable logistic regression included six variables: PHT, PoS, age, gender (male or female), injury type (blunt or penetrating), and transport mode (air or ground). The odds ratio (OR) for mortality was calculated for 1-minute, 10-minute, and 30-minute PHT intervals for each study population.

The mean PHT between all survivors and all nonsurvivors were compared for each study population using a two-sample t-test. To apply the methods of Petri et al., this comparison was also performed within five approximately equal sized patient groups stratified on the basis of ISS.[17]

Finally, the survival of each population was plotted across the four increasing intervals of PHT (minutes) used by Kleber et al.: < 30, 30-60, 61-90, >90.[16] The 30-minute time intervals used by Kleber et al. were used instead of those used by Di Bartolomeo et al in order to achieve greater significance in survival calculations than that achieved by Di Bartolomeo et al., which used 11-minute time intervals with each including only a small sample of patients.[18] The results of each analysis method for each study population were compared.

RESULTS

Characteristics of Study Populations

Of the 20,217 patients in the UVA trauma registry, 15,670 patients were transported from the scene by EMS. Of this population, 6,642 patients had a recorded GCS, RR, SBP, injury type, injury time, injury date, ED arrival time, and ED arrival date. Compared to those with complete data, the patient population with incomplete data included fewer males (59% < 61%; $p < 0.01$), had a greater average age (46 > 44; $p < 0.01$), and had a lower rate of penetrating injuries (92% < 94%; $p < 0.01$). The remaining variables did not differ significantly, including mortality ($p = 0.52$), PHT ($p = 0.71$), PoS ($p = 0.25$), and transport mode ($p = 0.69$).

Of the 6,642 patients who were transported by EMS from the scene and had complete data sets, 5,063 patients had a PHT within 0 and 120 minutes. These patients comprised the study population for the RMA and were used to represent the study population of Lerner et al., which did not use an acuity threshold. Of these 5,063 patients, 2,985 patients had an ISS ≥ 9 and were used to represent the Kleber et al. study population, 2,066 patients had an ISS ≥ 10 and were used to represent the Petri et al. study population, and 1,332 patients had an ISS > 15 and were used to represent the Di Bartolomeo et al. study population. Finally, 884 patients were adults (age > 15) with SBP ≤ 90 mmHg, GCS ≤ 12, RR < 10 or > 29 breaths/min, and/or an advanced airway intervention, and were used to simulate the Newgard et al. study population. The acuity threshold for each of the previous studies along with the number of patients who met the acuity threshold for both the original study and this study are shown in Table 1.

Table 1. Acuity threshold for the previous studies, with the number of patients who met the threshold for the original study and for this study.

Study Author	Population Acuity Threshold	Number of Patients Who Met Threshold	
		Original Study	This Study
Lerner et al.	none	1,877	5,063
Kleber et al.	all patients with ISS ≥ 9	20,078	2,985
Petri et al.	all patients with ISS ≥ 10	5,215	2,066
Di Bartolomeo et al.	all patients with ISS > 15	753	1,332
Newgard et al.	adults (age > 15) with ≥ 1 of the following: • SBP ≤ 90 mmHg • GCS ≤ 12 • RR < 10 or > 29 breaths/min • advanced airway intervention	3,656	884

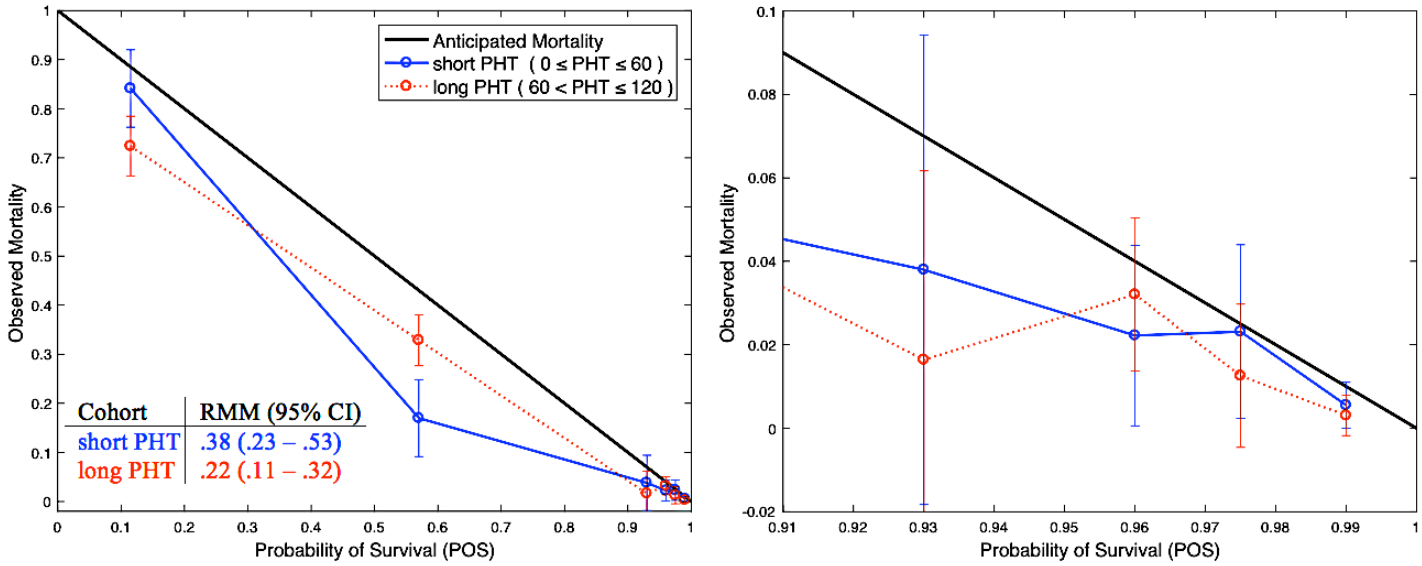
ISS, Injury Severity Score; *SBP*, systolic blood pressure; *GCS*, Glasgow Coma Scale; *RR*, respiratory rate.

Philip H. Schroeder, phs5eg@virginia.edu, Systems and Information Engineering, University of Virginia, 151 Engineer's Way, Charlottesville, VA 22904, USA.

Relative Mortality Analysis

The population of 5,063 patients was divided into six bins, summarized in Table 2. The short PHT cohort had fewer patients than the long PHT cohort for each bin. Thus, the short PHT cohort included only the minimum number of patients needed to ensure $E_b < .08$ for bin 1 and bin 2, to achieve the greatest resolution among the higher acuity patients (PoS < 91%), resulting in the PoS ranges (R_b) shown in Table 2.

As shown in Figure 1, the RMM values for the short PHT cohort and long PHT cohort do not significantly differ, with overlapping confidence intervals (CI). However, for bin 2, which contained patients with 23% ≤ PoS < 91%, the observed mortality for the long PHT cohort ($O_b = .328 \pm .052$) was significantly greater than that of the short PHT cohort ($O_b = .170 \pm .078$), as shown in Figure 1 and Table 2. Bin 2 comprised 9.9% of the UVA Trauma Center population and was the only bin with patients who benefited from reduced PHT.



(a) Full view of the RMPT analysis

(b) Enlarged view of the RMPT analysis for PoS > .91

Figure 1. Relative Mortality Performance Trend (RMPT) analysis across full spectrum of patient acuity and Relative Mortality Metric (RMM) for short pre-hospital time (PHT) and long PHT cohorts. 95% confidence intervals (CI) shown by error bars for the RMPT plot and in parentheses for the RMM values.

Table 2. Summary of bins for Relative Mortality Analysis.

bin	R_b	N_b		$O_b \pm E_b$	
		short PHT	long PHT	short PHT	long PHT
1	.00 - .23	63	105	.841 ± .079	.724 ± .061
2	.23 - .91	153	347	.170 ± .078	.328 ± .052
3	.91 - .95	79	122	.038 ± .056	.016 ± .045
4	.95 - .97	315	437	.022 ± .022	.032 ± .018
5	.97 - .98	216	318	.023 ± .021	.013 ± .017
6	.98 - 1.00	1269	1639	.006 ± .006	.003 ± .005

R_b, probability of survival range; N_b, number of patients in cohort; O_b, observed mortality; E_b, error value for 95% confidence interval; *PHT*, pre-hospital time.

Philip H. Schroeder, phs5eg@virginia.edu, Systems and Information Engineering, University of Virginia, 151 Engineer's Way, Charlottesville, VA 22904, USA.

Methods of Previous Analyses

As shown in Tables 3-5 and Figure 2, the analysis methods from Lerner et al., Kleber et al., Petri et al., Di Bartolomeo et al., and Newgard et al. yielded significant results only for the RMA bin 2 population, the population identified by the RMA to benefit from reduced PHT. None of the methods identified any significant relationship between PHT and mortality in each of the five study populations formed by the population selection methods of the five previous studies.

For the multivariable logistic regression (Table 3), PoS was the only continuous variable not normally distributed, so the variable was dichotomized at the median PoS value for each study population. The OR values for 1-minute, 10-minute, and 30- minute PHT intervals were only significant for RMA bin 2, each with a p-value < 0.01.

When comparing the mean PHT for survivors and nonsurvivors (Table 4) among the different populations, there was only a significant difference for the RMA bin 2 population, in which survivors had a lower mean PHT than nonsurvivors. As shown in Table 5, when the population created by the Petri et al. acuity threshold was stratified into ISS groups of approximately equal size, the resulting ISS intervals were 10-12, 13-15, 16-19, 20-26, and > 27. There was no significant difference in mean PHT between survivors and nonsurvivors for any of the ISS intervals.

Table 3. Multivariable logistic regression analysis of impact of pre-hospital time on mortality in each study population.*

Population	1-minute increments	10-minute increments	30-minute increments
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Lerner et al.	1.00 (0.99 – 1.00)	0.97 (0.93 – 1.02)	0.98 (0.85 – 1.13)
Kleber et al.	1.00 (0.99 – 1.01)	1.00 (0.95 – 1.05)	1.05 (0.89 – 1.24)
Petri et al.	1.00 (0.99 – 1.01)	0.99 (0.93 – 1.05)	1.01 (0.85 – 1.20)
Di Bartolomeo et al.	1.00 (0.99 – 1.01)	1.00 (0.95 – 1.05)	1.07 (0.88 – 1.30)
Newgard et al.	1.00 (0.99 – 1.01)	1.04 (0.96 – 1.13)	1.17 (0.93 – 1.48)
RMA bin 2	1.02 (1.01 – 1.03)	1.25 (1.13 – 1.37)	1.95 (1.47 – 2.60)

OR, Odds Ratio; *CI*, Confidence interval

*Multivariable logistic regression models included the following covariates: pre-hospital time, probability of survival, age, gender, injury type, and transport mode.

Table 4. Comparison of mean pre-hospital time (PHT) between survivors and nonsurvivors in each study population.

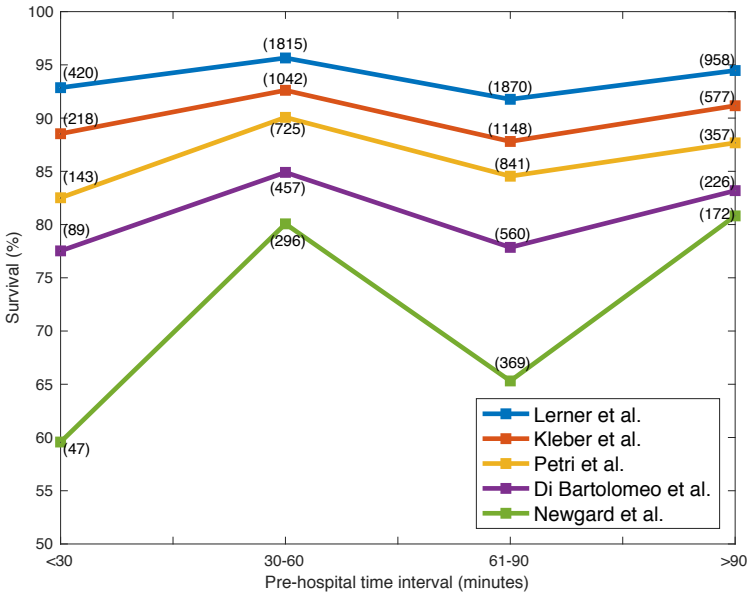
Population	Mean PHT (minutes)		p-value
	survivors	nonsurvivors	
Lerner et al.	66.69	67.49	0.59
Kleber et al.	67.83	68.08	0.87
Petri et al.	67.24	67.51	0.87
Di Bartolomeo et al.	67.51	67.69	0.91
Newgard et al.	69.56	67.69	0.31
RMA bin 2	68.04	76.88	< 0.01

Table 5. Comparison of mean pre-hospital time (PHT) between survivors and nonsurvivors across Injury Severity Score (ISS) subgroups.

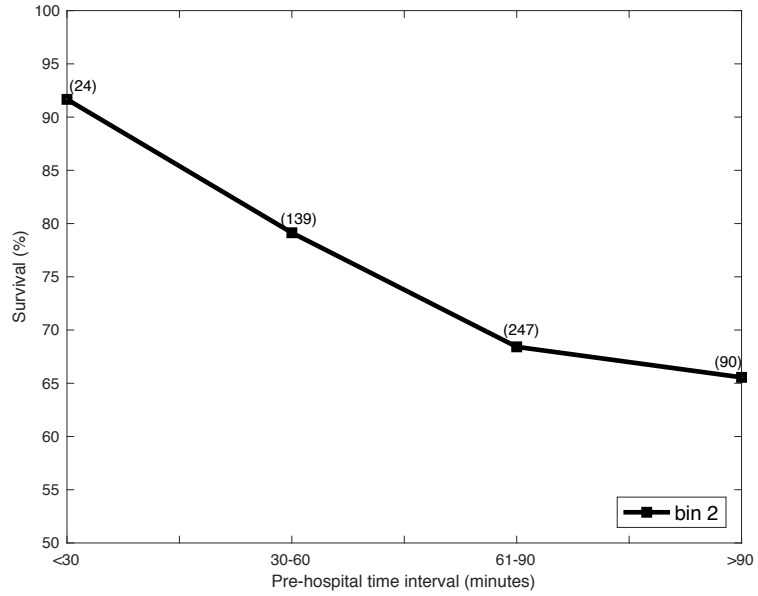
ISS	Number of Patients	Mean PHT (minutes)		p-value
		survivors	nonsurvivors	
10-12	312	66.54	54.10	0.38
13-15	422	67.05	76.30	0.41
16-19	458	68.54	65.24	0.65
20-26	432	67.01	67.96	0.76
> 27	442	66.58	67.89	0.54

Philip H. Schroeder, phs5eg@virginia.edu, Systems and Information Engineering, University of Virginia, 151 Engineer's Way, Charlottesville, VA 22904, USA.

Finally, the only population with a notable trend between survival and PHT was that of RMA bin 2, in which survival was negatively correlated with PHT (Figure 2b). The number of patients in each PHT interval is provided in parentheses within the plot.



(a) Plot of the five study populations created from the previous studies' population selection methods



(b) Plot of the bin 2 population from the Relative Mortality Analysis

Figure 2. Plot of patient survival across increasing intervals of pre-hospital time, with the number of patients in each time interval provided in parentheses.

LIMITATIONS

A significant portion of the UVA Trauma Center patient population did not have complete data. When comparing patients with complete data to those with incomplete data, there were no significant differences in mortality, patient acuity (PoS), PHT, or transport mode, but there were differences in gender ratios, age, and injury type. It is possible exclusion of these patients introduced bias. Furthermore, the reduced number of patients limited the resolution with which the high acuity patients could be evaluated in the RMA. The smaller the study population, the larger the PoS range must be for each bin to include enough patients to maintain statistical power in the observed mortality calculation. Due to this limitation, the PoS range of RMA bin 2 spanned from 23% to 91%. A more narrow PoS range would have allowed for greater precision in identifying which patients were most impacted by PHT. The limited number of patients also reduced the amount of patients who satisfied the acuity threshold of the previous studies. Three of the five representative study populations in this study contained fewer patients than the original study. This limitation, in addition to the absence of recorded response, on-scene, and transport times in the UVA trauma registry, restricted the extent to which the methods of Kleber et al., Petri et al. and Newgard et al. could be fully evaluated.

DISCUSSION

When applied to the UVA Trauma Center population, previous studies' methods all failed to identify patients who benefited from reduced PHT, just as they did in the original studies, while the RMA supported the "golden hour," identifying a patient subgroup with significantly lower mortality when transported to the hospital within one hour. In all, these results suggest that these previous studies' limitations in accounting for acuity have contributed to the disagreement in "golden hour" literature by precluding identification of patients who benefited from reduced PHT within their populations. That is, the failures of these previous studies to identify patients who benefited from reduced PHT likely resulted from their inadequate attempts to account for confounding effects of patient acuity within their populations, as opposed to the true absence of such patients.

As discussed, the acuity thresholds of these studies were intended to account for patient acuity by including only patients considered high acuity and, thus, thought to benefit the most from reduced PHT.[15-19] However, the results of the RMA demonstrate that even if the acuity thresholds were successful in isolating high acuity patients in these previous studies, they still would have failed to account for the confounding effects of acuity on the relationship between PHT and mortality among their patients. That is, contrary to assumptions made by previous studies, the RMA shows that severely high acuity patients (PoS < 23%) were not significantly impacted by PHT. A possible explanation for this observation is that these patients, due to the severity of their injury, would not survive regardless of how quickly they are transported to the hospital. Nonetheless, the RMA demonstrates that to properly account for the confounding effects of acuity, it is not sufficient to simply isolate a high acuity study population, as the correlation between PHT and mortality may

Philip H. Schroeder, phs5eg@virginia.edu, Systems and Information Engineering, University of Virginia, 151 Engineer's Way, Charlottesville, VA 22904, USA.

still be diluted by very high acuity patients. In fact, being that the affected subgroup identified by the RMA included patients with a PoS of up to 91%, the acuity thresholds of the previous studies may have even eliminated patients who were most impacted by PHT. In all, when acuity thresholds were used in attempt to isolate patients with severe injuries in previous studies, the patients for whom PHT was most important may have still been drowned out and/or may not have been even fully represented in the study population.

Although both Petri et al. and the RMA stratified patients on the basis of acuity, the methods of Petri et al. failed to support the "golden hour" for each patient subgroup while the RMA identified a subgroup that significantly benefited from reduced PHT. Two limitations in the methods of Petri et al. may have contributed to this difference in results. First, the ISS, Injury Severity Score, used by Petri et al. is a univariate metric and less comprehensive than PoS, Probability of Survival, in capturing patient acuity.[22] ISS incorporates only the highest three AIS, Abbreviated Injury Scale, values in its calculation. AIS is an anatomical scoring system and simply represents the perceived threat, on a scale of 1 to 6, of a specific injury to patient survival. The sole dependence of the ISS on AIS values renders it unhelpful as a triage tool when used alone.[22] As discussed, the TRISS calculated PoS incorporates both physiological and anatomical measures, including all of the triage metrics used by previous studies (age, GCS, SBP, RR, and ISS), within its calculation, providing for a more comprehensive representation of patient acuity than ISS alone.[21] A second potential cause of this difference may have been that the ISS ranges for the subgroups in Petri et al. were sized to ensure each subgroup was comprised of an approximately equal number of patients,[17] while the PoS ranges of each subgroup in the RMA were sized to achieve the greatest resolution among high acuity patients. These different approaches to sizing subgroups led to different distributions of patients, which may have contributed to the difference in results.

EMS agencies and pre-hospital providers have always faced the challenge of regulating resource expenditure and risk exposure to optimize the good for the communities they serve. This study demonstrated that the commitment to minimizing PHT must remain a priority for all trauma patients, despite the conclusions of previous studies.[15-19] Although only a subgroup (9.9%) of the patients within this study were identified to be significantly impacted by PHT, this group is still too ill-defined and the relationship between PHT and mortality is still too misunderstood to justify delaying transport of any given trauma patient.

Further work is needed to determine whether the subgroup identified by the RMA, bin 2, included all patients impacted by the "golden hour" and if all patients within this subgroup were in fact impacted by the "golden hour." More work is also needed to better elucidate how patient mortality changes across smaller intervals of PHT. These efforts would be better supported with a larger study population, which would provide freedom to create a larger number of bins within the high acuity population and to test a greater variety of pre-hospital time intervals. In addition, it would be insightful to use the RMA to evaluate how changes in the specific types of PHT (i.e., response time, on-scene time, and transport time) impact patient mortality.

In conclusion, this study provides a potential explanation for the current disagreement in literature regarding the "golden hour." Specifically, this study suggests that previous studies' limitations in accounting for acuity have contributed to the disagreement in literature by precluding identification of patients who benefited from reduced PHT within their trauma populations. The RMA was shown to overcome these limitations and, in doing so, demonstrated that the "golden hour" is significantly impactful for patients who are not low acuity (PoS > 91%) or severely high acuity (PoS < 23%).

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Address for correspondence: Jeffrey S. Young, MD, MBA; Director, University of Virginia Trauma Center; Medical Director, Subspecialties Service Line; Professor of Surgery, University of Virginia School of Medicine; 1300 Jefferson Park Avenue, Charlottesville, VA 22903, (434) 982-3549, jsy2b@hscmail.mcc.virginia.edu

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Philip H. Schroeder, phs5eg@virginia.edu, Systems and Information Engineering, University of Virginia, 151 Engineer’s Way, Charlottesville, VA 22904, USA.