

ORIGINAL RESEARCH



Association between prehospital intravenous fluid administration with oxygen supplementation and the delta shock index for trauma-suspected shock without hypoxia

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Abstract

Background: This study aimed to examine the associations between prehospital intravenous (IV) fluid administration with oxygen (O₂) supplementation and the shock index in trauma patients suspected of having shock without hypoxia. **Methods:** This study analyzed data from an international multicenter trauma database from 2015 to 2020. We analyzed adult trauma patients transported by emergency medical service (EMS) personnel with an initial shock index more than or equal to 1.0. A delta shock index (DSI) of 0.1 or less was the primary outcome. Study participants were categorized into 3 groups: IV fluid with O₂, IV fluid only and no IV fluid. After adjusting for confounders, adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were computed using multivariate logistic regression. **Results:** Among 2019 patients, 1370 were not receiving IV fluid, 157 were receiving IV fluid only, and 492 received IV fluid with O₂. IV fluid with O₂ patients had a greater proportion of males (76.4%), and DSI was -0.27 for IV fluid and O₂, -0.26 for IV fluid only, and -0.21 for no IV fluid ($p < 0.01$). Compared to no IV fluid, there was no significant association between IV fluid with O₂ group and a DSI equal to or less than 0.1. AOR (95% CI) was 1.38 (0.85–2.23) for IV fluid with O₂ and 0.94 (0.65–1.35) for IV fluid only. **Conclusions:** No significant association was found between IV fluid administration and DSI in trauma patients with suspected shock without hypoxia at the scene, even when oxygen supplementation was added.

Keywords

Trauma; Shock; Emergency medical services; Intravenous fluid infusion; Oxygen inhalation therapy

1. Introduction

Trauma is a major public health concern worldwide [1]. There are 64 deaths per 100,000 people in lower-middle- and low-income countries in the Asia Pacific region, which is approximately twofold greater than in countries in the Organization for Economic Cooperation and Development (OECD) [2]. Trauma has a far greater financial impact than just the immediate medical expenses involved; it also has repercussions on the individual, family, and society as a whole, including lost productivity [3].

Intra transport stabilization has been crucial for improving clinical outcomes in trauma patients [4, 5]. The correlation between shock index and prehospital trauma care outcomes is widely recognized [6]. In particular, prior research has examined the delta shock index (DSI) as a surrogate marker for deterioration and has shown promise in predicting mortality or

surgical intervention among trauma patients in the emergency department (ED) [6–9]. Owing to its relative ease of measurement, it can be assumed that the DSI could be considered an index of stabilization during transport [10].

Traumatic death is potentially preventable through the implementation of early and high-quality resuscitation, with a crucial emphasis on initiating prehospital critical care [10]. Although there has been debate regarding the effects of prehospital intravenous fluid administration on traumatic shock [11], positive intra transport stabilization has been shown [12]. Oxygen (O₂) supplementation for severely injured trauma patients, regardless of pulse oximeter oxygen saturation (SpO₂), is frequently disregarded [13]. Peripheral oxygen saturation in a patient in shock may remain within the normal range even if oxygen delivery is compromised [14]. In a study by Kirkman, maintaining the SpO₂ level at 95% following blast injury in a porcine model of controlled or uncontrolled bleeding

was associated with prolonged survival times, as opposed to breathing room air [15]. It has not yet been determined, though, if oxygenation helps traumatic shock patients who exhibit normoxia.

In contrast to patients who receive only IV fluid, we hypothesized that traumatic shock patients who receive prehospital IV fluid administration with O₂ supplementation and sustain normal SPO₂ might have a lower DSI during EMS transportation. This study investigated the association between prehospital IV fluid administration with O₂ supplementation and DSI in trauma patients suspected of having shock without hypoxia.

2. Methods

2.1 Study design and setting

Data for this retrospective, cross-sectional study were gathered from the Pan-Asian Trauma Outcomes Study (PATOS) Registry, an international, multicenter, and population-based trauma database with data from participating hospitals in Asia-Pacific countries. Data were collected from 2015 to 2020 and integrated using an electronic data capture system hosted by the study coordinating center [16]. It was released in 2021 after preprocessing and quality management. Emergency medical systems (including EMS services) vary from country to country, as do population characteristics (the proportion of the urban population ranges from 32.7 to 93.5). Furthermore, these six countries have different health indices (the age-standardized injury mortality rate ranges from 40 to 116, and the number of years of life lost ranges from 20,054,785) in varying medical settings, such as the designated trauma center level [17, 18].

2.2 Data source and collection

PATOS collected demographic, injury epidemiology, prehospital, hospital, and patient outcome information. The PATOS Clinical Research Network (CRN) reviewed background information from existing registries and followed the World Health Organization (WHO) guidelines for injury surveillance [19].

Prehospital data were collected from ambulance run sheets or EMS dispatch records. Hospital medical records were used to obtain hospital records and patient outcome data. Training modules were developed to educate all personnel involved in data registration to data quality uniformity and consistency. Electronic data capture was used to capture all the data. The PATOS Data Quality Management Committee (QMC) monitored invalid and incomplete data forms and provided timely feedback to participating hospitals. For data corrections, participating hospitals had two weeks to respond to the PATOS Data QMC reports.

2.3 Study population

All trauma patients enrolled in the database between 2015 and 2020 were initially screened. Under 18 and over 105 years old (considered unusual elderly [20]), patients suffering from prehospital cardiac arrest, transferred from another hospital, not transported by EMS, patients with nontraumatic injuries, hypoxia (SpO₂ less than 90%) at the scene, and patients with

incomplete exposure and outcome information were excluded. A shock index (SI) equal to or greater than 1.0 at the scene, calculated as the heart rate divided by systolic blood pressure, was also used to select patients with suspected shock [21–23].

2.4 Outcomes

A delta shock index (DSI) of 0.1 or less was the primary outcome. The DSI was calculated using the shock index at the scene and upon arrival at the ED (ED heart rate/ED systolic blood pressure/scene heart rate/scene systolic blood pressure). EMS personnel and triage nurses measured all vital signs used to calculate shock indices. A DSI cutoff value of 0.1 was determined based on values reported in previous studies that examined its association with mortality, *i.e.*, the need for interventions [21–23]. A DSI of less than or equal to 0.1 could be considered a surrogate marker for intra transport stabilization. Secondary outcomes collected from medical records included a shock index at the ED entrance below 1.0 and survival to discharge. A cutoff value of 1.0 has been used in previous studies to indicate an association between ED shock index and mortality in trauma patients [24]. Survival to discharge was determined according to the patient's status at the time of discharge from the hospital.

2.5 Main exposures and variables

Prehospital IV fluid administration with O₂ supplementation was the main exposure. We collected data on demographics and preexisting comorbidities, prehospital information (mechanism of injury, alcohol consumption status, vital signs and mental status, and prehospital EMS procedures, including airway management, O₂ supplementation, and fluid administration), in-hospital information (vital signs, mental status and ED management, such as endotracheal intubation, blood transfusion, surgical management and angiographic embolization), clinical outcomes (injury severity score, intensive care unit admission and survival to discharge) and shock indices at the scene and upon arrival at the ED.

2.6 Statistical analyses

Study groups were categorized into IV fluid with O₂, IV fluid only, and no IV fluid groups. Demographic and clinical findings were analyzed and compared. Categorical variables were presented as numbers and percentages and compared using the Chi-square test. Continuous variables expressed as median and interquartile range (IQR), were compared using the Wilcoxon rank-sum test. Logistic regression analysis was used to evaluate the association between prehospital IV fluid administration with or without O₂ supplementation and a DSI equal to or less than 0.1. The reference group was patients without IV fluid administration. Confounders were chosen because they were determined after the main exposure and affected the outcome. After adjusting for potential confounders—age groups (18–44 years, 45–64 years, older than 64 years), sex, medical history, injury mechanism (traffic accident, fall or slip, blunt force, others), alcohol consumption, systolic blood pressure at the scene (hypotension, hypertension, and within the normal range), hypoxia at the scene and mental status at the scene

(alert, verbal response, pain response and unresponsiveness)—adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were calculated for outcomes. Due to the hierarchical structure of different countries, we conducted multilevel analysis using a generalized linear mixed-effects model (each district of the EMS was served as a random-intercept variable). A sensitivity analysis was conducted on cohorts with injury severity scores greater than 8, indicating moderate to major trauma. Using all available data from the database, we did not perform a separate sample size calculation. Data analyses were performed using Statistical Analysis System version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

114,100 patients from the PATOS database were screened over the study period. Pediatric patients, patients aged greater than 105 years ($n = 10,864$), non-EMS transport patients ($n = 37,428$), prehospital cardiopulmonary resuscitation (CPR) patients ($n = 1059$), patients with hypoxia at the scene ($n = 7008$), patients with a field shock index <1.0 ($n = 55,409$), patients with missing exposure data ($n = 114$), and patients with missing shock index data ($n = 199$) were excluded. A total of 2019 patients were included in the final analysis. Patients were grouped into 3 groups: control ($n = 1370$), IV fluid only ($n = 157$), and IV fluid with O_2 ($n = 492$) (Fig. 1).

Demographic and clinical findings of patients were described in Tables 1-1,1-2. IV fluid with O_2 patients were more likely to be male (76.4%), with a higher proportion of traffic accident victims (64.0%) and a lower proportion of tachycardia victims (60.4%). Airway management by

EMS personnel was significantly more common ($p < 0.01$). DSI was -0.27 for the IV fluid and O_2 group, -0.26 for the IV fluid-only group, and -0.21 for the no IV fluid group ($p < 0.01$). ED shock or field shock indices did not differ across all groups ($p = 0.14$ and 0.10 , respectively). Based on the multilevel multivariable logistic regression analysis, compared to the no IV fluid group, there was no significant association with a DSI equal to or less than 0.1. AOR (95% CI) was 1.38 (0.85–2.23) for the IV fluid with O_2 group, and 0.94 (0.65–1.35) for the IV fluid only group (Table 2). According to sensitivity analysis, the IV fluid with O_2 group had a significantly greater probability of having a DSI of 0.1 or less than the no IV fluid group in the cohort without hypoxia. AORs (95% CIs) were 2.00 (1.46–2.73) for the IV fluid with O_2 group, and 1.07 (0.66–1.71) for the IV fluid only group than the no IV fluid group (Table 3). Prehospital IV fluid administration with O_2 supplementation was not associated with an ED shock index of 0.1 or less. Compared with no IV fluid, O_2 supplementation was associated with a lower probability of survival to discharge.

4. Discussion

There was no significant association between prehospital IV fluid administration with O_2 supplementation and DSI in trauma patients with suspected shock without hypoxia. IV fluid without O_2 supplementation also showed no significant association. A statistically significant association was only observed for IV fluid with O_2 supplementation in patients with moderate to major trauma, with injury severity scores greater than 8. ED shock index lower than 1.0 had no

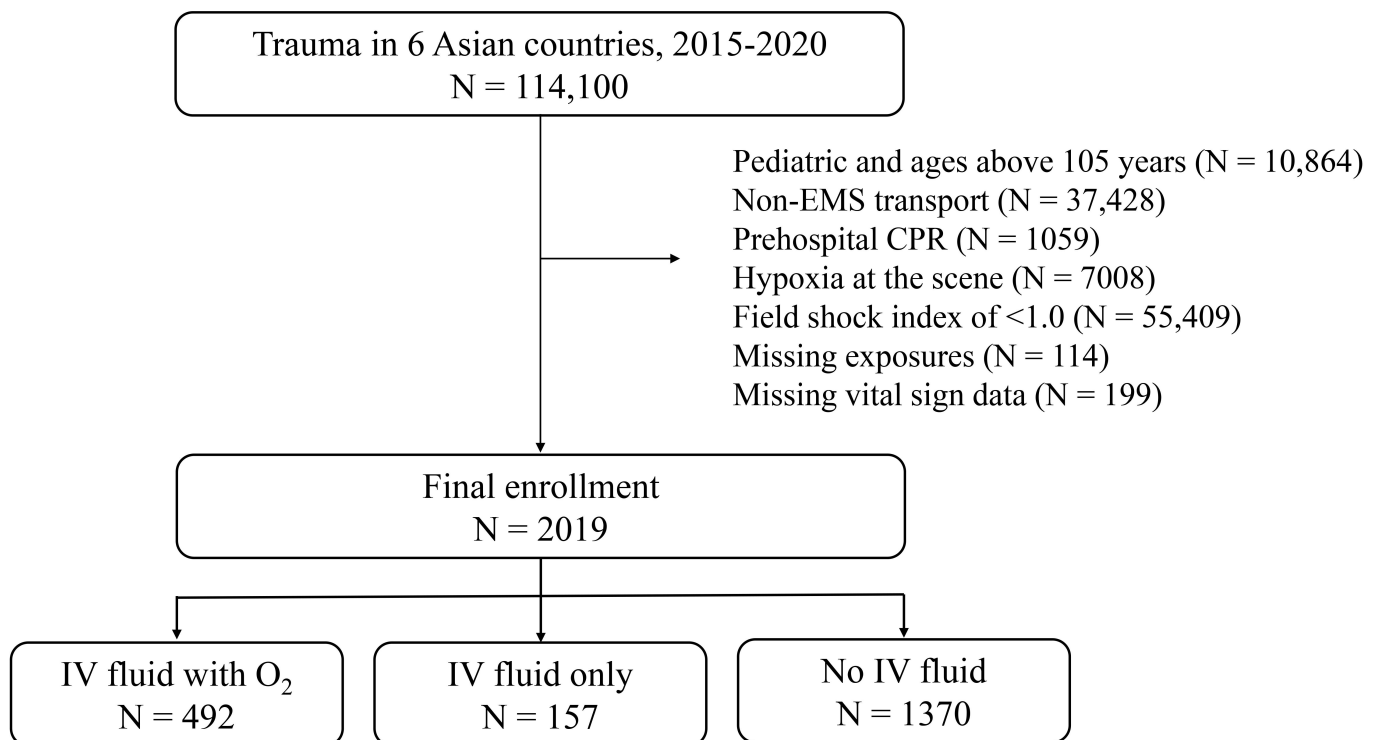


FIGURE 1. Flowgram of the study population. EMS, emergency medical services; CPR, cardiopulmonary resuscitation; IV, intravenous; O_2 , oxygen.

TABLE 1-1. Demographics and clinical findings according to the prehospital intravenous fluid management with oxygen supplementation.

| | Total N (%) | No IV fluid N (%) | IV fluid only N (%) | IV fluid with O ₂ N (%) | <i>p</i> -value |
|---|----------------|----------------------|------------------------|---------------------------------------|-----------------|
| Total | 2019 | 1370 (67.9) | 157 (7.8) | 492 (24.4) | |
| Demographic information | | | | | |
| Age, yr, median (IQR) | 39 (25–56) | 40 (27–58) | 30 (22–47) | 36 (24–52) | <0.001 |
| Age group, yr | | | | | |
| 18–44 | 1177 (58.3) | 751 (54.8) | 114 (72.6) | 312 (63.4) | |
| 45–64 | 543 (26.9) | 395 (28.8) | 27 (17.2) | 121 (24.6) | <0.001 |
| ≥65 | 299 (14.8) | 224 (16.4) | 16 (10.2) | 59 (12.0) | |
| Sex, Male | 1347 (66.7) | 854 (62.3) | 117 (74.5) | 376 (76.4) | <0.001 |
| Past medical history | 240 (11.9) | 181 (13.2) | 15 (9.6) | 44 (8.9) | 0.028 |
| Prehospital information | | | | | |
| Mechanism on injury | | | | | |
| TA | 943 (46.7) | 528 (38.5) | 100 (63.7) | 315 (64.0) | |
| Fall | 547 (27.1) | 421 (30.7) | 20 (12.7) | 106 (21.5) | <0.001 |
| Blunt | 269 (13.3) | 229 (16.7) | 9 (5.7) | 31 (6.3) | |
| Others | 260 (12.9) | 192 (14.0) | 28 (17.8) | 40 (8.1) | |
| Alcohol drunken | 559 (27.7) | 424 (30.9) | 38 (24.2) | 97 (19.7) | <0.001 |
| Systolic blood pressure, mmHg, median (IQR) | | | | | |
| Hypotension | 420 (20.8) | 221 (16.1) | 56 (35.7) | 143 (29.1) | <0.001 |
| Heart rate, beat per min, median (IQR) | | | | | |
| Tachycardia | 1567 (77.6) | 1156 (84.4) | 114 (72.6) | 297 (60.4) | <0.001 |
| Mental status | | | | | |
| Alert | 1514 (75.0) | 1175 (85.8) | 125 (79.6) | 214 (43.5) | |
| Verbal response | 116 (5.7) | 61 (4.5) | 7 (4.5) | 48 (9.8) | |
| Pain response | 79 (3.9) | 31 (2.3) | 6 (3.8) | 42 (8.5) | <0.001 |
| Unresponsiveness | 44 (2.2) | 23 (1.7) | 1 (0.6) | 20 (4.1) | |
| Missing | 266 (13.2) | 80 (5.8) | 18 (11.5) | 168 (34.1) | |
| Airway management | 421 (20.9) | 81 (5.9) | 6 (3.8) | 334 (67.9) | <0.001 |
| Oxygen supplement | 755 (37.4) | 263 (19.2) | - | 492 (100.0) | <0.001 |
| Fluid administration | 649 (32.1) | - | 157 (100.0) | 492 (100.0) | <0.001 |

IV, intravenous; O₂, oxygen; IQR, interquartile range; TA, traffic accident.

TABLE 1-2. Demographics and clinical findings according to the prehospital intravenous fluid management with oxygen supplementation.

| | Total N (%) | No IV fluid N (%) | IV fluid only N (%) | IV fluid with O ₂ N (%) | <i>p</i> -value |
|---|----------------|----------------------|------------------------|---------------------------------------|-----------------|
| Total | 2019 | 1370 (67.9) | 157 (7.8) | 492 (24.4) | |
| In-hospital information | | | | | |
| Systolic blood pressure, mmHg, median (IQR) | | | | | |
| Hypotension | 294 (14.6) | 189 (13.8) | 26 (16.6) | 79 (16.1) | 0.362 |
| Heart rate, beat per min, median (IQR) | | | | | |
| Tachycardia | 896 (44.4) | 534 (39.0) | 81 (51.6) | 281 (57.1) | <0.001 |
| Oxygen saturation, %, median (IQR) | | | | | |
| Hypoxia | 51 (2.5) | 31 (2.3) | 2 (1.3) | 18 (3.7) | <0.001 |

TABLE 1-2. Continued.

| | Total N (%) | No IV fluid N (%) | IV fluid only N (%) | IV fluid with O ₂ N (%) | <i>p</i> -value |
|-------------------------------------|-------------------------|------------------------|------------------------|---------------------------------------|-----------------|
| Mental status | | | | | |
| Alert | 1547 (76.6) | 1102 (80.4) | 125 (79.6) | 320 (65.0) | |
| Verbal response | 184 (9.1) | 96 (7.0) | 19 (12.1) | 69 (14.0) | |
| Pain response | 102 (5.1) | 57 (4.2) | 6 (3.8) | 39 (7.9) | <0.001 |
| Unresponsiveness | 44 (2.2) | 18 (1.3) | 1 (0.6) | 25 (5.1) | |
| Missing | 142 (7.0) | 97 (7.1) | 6 (3.8) | 39 (7.9) | |
| Intubation | 225 (11.1) | 112 (8.2) | 19 (12.1) | 94 (19.1) | <0.001 |
| Transfusion | 438 (21.7) | 277 (20.2) | 42 (26.8) | 119 (24.2) | 0.052 |
| Any surgery | 902 (44.7) | 420 (30.7) | 89 (56.7) | 393 (79.9) | <0.001 |
| Any angiographic embolization | 521 (25.8) | 151 (11.0) | 57 (36.3) | 313 (63.6) | <0.001 |
| Clinical outcomes | | | | | |
| Injury severity score, median (IQR) | 17 (11–27) | 17 (9–27) | 22 (17–34) | 19 (11–29) | 0.002 |
| ICU admission | 1477 (73.2) | 1016 (74.2) | 113 (72.0) | 348 (70.7) | 0.319 |
| Survival to discharge | 1923 (95.2) | 1324 (96.6) | 150 (95.5) | 449 (91.3) | <0.001 |
| Shock indexes | | | | | |
| ED shock index, median (IQR) | 0.89 (0.71–1.08) | 0.91 (0.73–1.08) | 0.9 (0.71–1.12) | 0.86 (0.67–1.09) | 0.143 |
| Field shock index, median (IQR) | 1.08 (1.01–1.21) | 1.08 (1.02–1.19) | 1.1 (1.03–1.24) | 1.08 (1–1.26) | 0.102 |
| Delta shock index, median (IQR) | –0.22 (–0.39– –0.03) | –0.21 (–0.38––0.02) | –0.26 (–0.43––0.02) | –0.27 (–0.41––0.06) | 0.003 |

IV, intravenous; O₂, oxygen; IQR, interquartile range; ED, emergency department; ICU, intensive care unit.

TABLE 2. Multivariable logistic regression analysis according to the prehospital intravenous fluid management with oxygen supplementation.

| Outcomes | n/N (%) | Univariable analysis OR (95% CI) | Multivariable analysis Adjusted OR (95% CI) |
|--------------------------------------|------------------|-------------------------------------|--|
| Delta shock index ≤0.1 | | | |
| No IV fluid | 1209/1370 (88.2) | Reference | Reference |
| IV fluid only | 137/157 (87.3) | 0.79 (0.54–1.17) | 0.94 (0.65–1.35) |
| IV fluid with O ₂ | 452/492 (91.9) | 1.16 (0.68–1.96) | 1.38 (0.85–2.23) |
| ED Shock index lower than 1.0 | | | |
| No IV fluid | 872/1370 (63.6) | Reference | Reference |
| IV fluid only | 93/157 (59.2) | 0.84 (0.56–1.26) | 1.02 (0.68–1.52) |
| IV fluid with O ₂ | 315/492 (64.0) | 0.96 (0.63–1.46) | 1.11 (0.72–1.73) |
| Survival to discharge | | | |
| No IV fluid | 1324/1370 (96.6) | Reference | Reference |
| IV fluid only | 150/157 (95.5) | 0.62 (0.22–1.80) | 0.63 (0.20–1.96) |
| IV fluid with O ₂ | 449/492 (91.3) | 0.32 (0.18–0.57) | 0.52 (0.29–0.94) |

OR, odds ratio; CI, confidence interval; IV, intravenous; O₂, oxygen; ED, emergency department.

Multivariable analysis adjusted age group, sex, past medical history, mechanism of injury, alcohol drunken, blood pressure status and heart rate status at the scene, mental status at the scene and injury severity score.

TABLE 3. Sensitivity analysis for patients with injury severity score over 8.

| Outcomes | n/N (%) | Univariable analysis OR (95% CI) | Multivariable analysis Adjusted OR (95% CI) |
|-------------------------------|----------------|-------------------------------------|--|
| Delta shock index ≤ 0.1 | | | |
| No IV fluid | 309/404 (76.5) | Reference | Reference |
| IV fluid only | 48/61 (78.7) | 0.96 (0.66–1.40) | 1.07 (0.66–1.71) |
| IV fluid with O ₂ | 156/178 (87.6) | 1.80 (1.28–2.53) | 2.00 (1.46–2.73) |
| ED Shock index lower than 1.0 | | | |
| No IV fluid | 190/404 (47.0) | Reference | Reference |
| IV fluid only | 23/61 (37.7) | 0.56 (0.28–1.10) | 0.65 (0.35–1.22) |
| IV fluid with O ₂ | 97/178 (54.5) | 1.13 (0.75–1.68) | 1.30 (0.80–2.12) |
| Survival to discharge | | | |
| No IV fluid | 372/404 (92.1) | Reference | Reference |
| IV fluid only | 57/61 (93.4) | 0.91 (0.31–2.66) | 0.75 (0.24–2.37) |
| IV fluid with O ₂ | 159/178 (89.3) | 0.58 (0.38–0.87) | 0.58 (0.39–0.87) |

OR, odds ratio; CI, confidence interval; IV, intravenous; O₂, oxygen; ED, emergency department.

Multivariable analysis adjusted age group, sex, past medical history, mechanism of injury, alcohol drunken, blood pressure status and heart rate status at the scene, mental status at the scene and injury severity score.

significant effect on survival to discharge, while IV fluid with O₂ supplementation did. Further investigations should be performed to clarify the additive effect of O₂ supplementation on organ perfusion in trauma patients.

Hyperoxia plays a crucial role in acute circulatory shock management. Especially after trauma 26, compensating for O₂ debt (an imbalance between O₂ supply and requirements) is essential to survival [25]. Current trauma guidelines on O₂ therapy, however, lack clarity and excessive O₂ administration has even been reported to be harmful in certain patient populations [26]. Additionally, the systematic review found no evidence for using supplemental O₂ in spontaneously breathing trauma patients [26]. In a study of a specific group, such as patients with traumatic brain injury, despite normal O₂ saturation, prehospital low-flow O₂ administration was associated with lower in-hospital mortality than no O₂ administration [27]. In spite of different schools of thought about the benefits of prehospital O₂ [26–28] and fluid administration [11, 29, 30] for trauma patients, the results of this study may provide some clues for participants with more severe injuries.

Prehospital EMS management may not necessarily improve survival outcomes. This aligns with previous studies that showed a positive association between aggressive EMS management and increased mortality rates [29]. EMS personnel may administer medical procedures and interventions based on unmeasurable severity assessment results during prehospital care. Even when SpO₂ was normal, patients that received O₂ supplementation in addition to IV fluids tended toward a lower DSI and shock index at the ED entrance than those who only received IV fluids. Patients with traumatic shock may benefit from routine O₂ supplementation. In patients suspected of having severe trauma, prehospital fluid administration with oxygen supplementation may be beneficial. A high level of

clinical suspicion should also be maintained by EMS personnel for patients whose shock index is initially elevated. There should be further large-scale clinical and preclinical studies addressing these limitations.

This study had several limitations. First, trauma-suspected shock was assessed based on the shock index at the scene, which may have introduced potential selection bias. Possibly more patients without definite shock were included in the analysis, resulting in unclear associations. A retrospective database was used to calculate DSI, which may have produced unintended selection bias. Patients suspected of severe trauma are typically monitored by EMS personnel, but protocols vary by region and patient monitoring was not standardized. Hypoxic conditions can also vary according to patient age or medical comorbidities, but cannot be adjusted. Furthermore, patients with cardiac arrest were excluded due to an unclear DSI. This limits the generalizability and application of the results to the most severe cases. Second, we defined the DSI as a surrogate marker of intra transport stabilization, but it has not been well validated in large-scale studies. Although the DSI is known to be associated with clinical outcomes in previous trauma research, this is still a significant limitation. Third, a detailed trauma care protocol was not included in the analysis. The prehospital and hospital treatment protocols vary, as do the capacities of Asian countries to treat trauma patients. The type of management for each patient could not be confirmed. For patients with bleeding or hypotension, oxygen inhalation and IV fluid administration have generally been recommended for patients with respiratory distress or weak breathing. Furthermore, as a retrospective observational study, there may be potential unmeasurable confounders. Databases lacked detailed information about injuries or factors affecting physiological parameters, such as weather. When applying

the study findings to other trauma management settings, these factors need to be carefully considered.

5. Conclusions

DSI was not significantly lower in trauma patients with shock without hypoxia when prehospital IV fluids were administered with oxygen supplementation. This may increase organ perfusion, but more research is needed to determine the impact and evaluate the potential for its use in prehospital trauma care.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

KDGN and KHK—had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; acquisition, analysis, or interpretation of data; drafting of the manuscript; statistical analysis. JHP, SDS and KHK—study concept and design. JHP, YSR, KJS, WCC and FJG—critical revision of the manuscript for important intellectual content. KJS, SDS, WCC and FJG—administrative, technical, or material support. KJS and SDS—study supervision. All authors have approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study complied with the Declaration of Helsinki. This study was ethically approved by the Seoul National University Hospital Institutional Review Board (IRB No. 1509-045-702). Need of informed consent was waived by Institutional Review Board.

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CONFLICT OF INTEREST

No authors have other relationships, conditions or circumstances that present potential conflicts of interest.

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