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Development and Validation of a Novel Shock Diagnosis and Treatment Protocol Based on Ultrasound Visual Information

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基于超声可视化信息的新休克诊疗流程的建立和验证

中文摘要

研究背景：

休克是重症患者的常见致死原因之一，具有高发病率和高死亡率。全球范围内，休克的总体死亡率可达 30%-50%，其中主要类型包括分布性休克、低血容量性休克、心源性休克和梗阻性休克。每种类型的休克病因各异，治疗策略也有所不同，个性化的诊疗路径对休克患者的有效管理至关重要。早期识别和快速干预是改善休克患者预后的关键。然而，普通病房的休克管理面临诸多挑战，受限于设备和资源，休克患者的治疗仍然不规范，缺乏实时监测和标准化的诊疗流程，导致无法及时正确识别和处理休克患者。对于普通病房确诊的休克患者，通常需要紧急转运至 ICU 进行专业救治。然而，转运时机如何影响患者预后，尚无系统性研究。转运至 ICU 的时机对于休克患者的预后具有潜在影响，在普通病房是否给予正确及时的治疗，转入 ICU 后是否及时进行超声评估但目前临床上缺乏系统性证据明确这一关联。因此，本研究的第一部分通过回顾性队列研究，探讨休克病人转移到 ICU 的时间与患者预后之间的相关性，明确早期使用超声对诊疗休克患者辅助作用，并筛选影响休克患者治疗效果的核心指标为优化早期诊疗策略提供依据。 即便在 ICU 内，如何快速精准地识别休克类型并提供个性化治疗仍是临床挑战。尽管重症超声已作为无创床旁监测工具广泛应用于休克的评估中，但目前临床上缺乏将其与其他诊疗数据整合的系统化方案。因此，本研究提出并验证了基于重症超声的个性化休克评估方案——OPACCUS 方案，旨在整合病因管理、血流动力学评估及机体反应干预，为休克患者提供更精准的治疗路径。

研究目的：

1. 旨在系统评估普通病房休克患者转移至ICU的时机对休克患者预后的影

响，探索早期使用超声辅助休克诊断及治疗的价值，同时筛选出与休克患者预后相关的核心诊疗指标(临床指标及超声指标)，并分析普通病房治疗不规范与患者预后之间的关联。这一过程为后续开发并验证基于超声可视化信息的新休克诊疗流程提供理论依据。

2. 开发并验证基于可视化信息的新休克诊疗流程评估方案（OPACCUS），整合重症超声和临床数据，建立以病因管理、精细血流动力学治疗和机体反应干预为核心的诊疗流程，改善休克患者的预后。

3. 通过多中心研究评估OPACCUS方案在临床中的应用效果，探讨其对休克患者预后（如死亡率、住院时间、费用等）的影响，验证其在复杂临床情境下的可操作性与有效性。

4. 推动休克诊疗流程的标准化与优化，通过对OPACCUS方案的实施与改进，针对休克病人提出具体的临床实践建议，提升休克病人管理的精准性和效率。

材料和方法：

本研究分为两部分，旨在系统评估普通病房休克患者转移至 ICU 的时机对预后的影响，探索早期使用超声诊疗休克的重要性，筛选休克诊治的核心指标，为优化休克患者的早期诊疗策略提供依据。同时，本研究还开发方案并验证了基于可视化信息的 OPACCUS 方案在休克管理中的应用效果。

第一部研究为回顾性队列研究，数据来源于四川大学华西医院在 2019 年 1 月 1 日至 2024 年 1 月 31 日期间由普通病房转移至 ICU 的休克患者。根据患者从普通病房转移到 ICU 的时间，将其分为三组：Group 1（转移时间<3 小时）、Group 2（转移时间 3-6 小时）、Group 3（转移时间>6 小时）。这些分组主要基于休克管理的关键时间窗口，重点关注早期（3 小时内）和适时（6 小时内）的干预策略。我们首先对三组患者的基线特征进行了比较。为了评估不同转移时间对休克患者住院死亡率的影响，采用 Kaplan-Meier 生存曲线分析，并通过 Log-

rank 检验比较三组之间的生存差异。此外，使用逻辑回归模型分析了转移时间与住院死亡率和 28 天死亡率之间的关系。数据分析还包括限制性立方样条回归模型(Restricted Cubic Spline, RCS)和受试者工作特征(Receiver Operating Characteristic Curve, ROC)曲线，用于评估转移时间作为预后指标的效能。为了评估早期使用超声对休克患者住院死亡率的影响，采用 Kaplan-Meier 生存曲线分析及逻辑回归模型分析与住院死亡率和 28 天死亡率之间的关联。最后建立预测休克患者院内死亡率的模型，通过单因素和多因素逻辑回归分析确定影响因素，并通过 ROC 曲线、Hosmer-Lemeshow 检验、校准曲线和决策曲线评估模型性能。

可视化 OPACCUS 诊疗方案的验证与应用

OPACCUS 方案的建立背景与设计通过第一部分的回顾性分析，验证了早期转移至 ICU 的重要性后，明确了开发基于超声可视化信息的新休克诊疗流程（OPACCUS）的必要性。OPACCUS 方案旨在整合病因管理、血流动力学评估和机体反应干预，以实现精细化标准休克管理。OPACCUS 方案的开发经历了多轮专家讨论，达成共识并不断修改校准，最终形成了该方案。

方案开发建立后，研究团队对多中心的 ICU 医生进行了系统化的培训，确保主治医生能够充分理解和使用 OPACCUS 方案。方案的执行过程包括通过重症超声及其他临床信息，对休克的病因、血流动力学和机体反应进行评估。基于此信息，OPACCUS 方案为医生提供新休克的治疗路径。

第二部研究为多中心前瞻性观察性队列真实世界研究、旨在验证 OPACCUS 方案的应用效果。研究对象为 2022 年 10 月至 2024 年 2 月期间中国西南地区 20 家医院 ICU 中的休克患者。本研究已获得四川大学华西医院伦理委员会的批准。所有参与者在纳入研究前均签署了知情同意书，以确保参与者的知情权和自愿权。记录患者的基本信息、传统血流动力学评估指标及治疗方案，评估 OPACCUS 方案在不同单位休克患者中的使用情况。鼓励各中心使用 OPACCUS 评估方案，但具体应用由主治医师决定。根据 OPACCUS 方案的执行率，将患者分为三组：完全执行组（执行率=100%）、中等执行组（执行率 50%

至 100%）和低执行组（执行率 < 50%）。主要观察终点为 30 天死亡率；次要结局包括大循环纠正时间、微循环纠正时间、ICU 住院时间（ICU LOS）、住院天数、呼吸机使用天数、ICU 费用及住院总费用等。首先比较三组基线指标，然后使用 Kaplan-Meier 生存曲线分析 30 天死亡率，并通过 Log-rank 检验、Fleming 检验和 Landmark 检验评估三组之间的 30 天死亡风险差异。进一步使用受限平均生存时间（Restricted Mean Survival Time, RMST）回归分析进行单因素和多因素分析。

结果：

第一部分研究结果：共纳入 3,535 名从普通病房转移至 ICU 的休克患者，平均年龄为 56.4±15.3 岁，男性占 65.5%（2,317 人），女性占 34.5%（1,218 人）。患者的平均住院时间为 21.5±21.7 天，ICU 住院时间为 7.77±13 天。总住院死亡率为 24.0%，休克的平均持续时间为 39.6±29.3 小时。休克类型分布为：分布性休克 2,392 人（67.7%）、低容量性休克 1,099 人（31.1%）、心源性休克 123 人（3.48%）、梗阻性休克 98 人（2.77%）。分布性休克中，脓毒性休克占多数（64.6%），而低容量性休克中，出血性休克占 15.0%。患者根据转移时间分为三组：第一组（<3 小时，n=2,849）、第二组（3-6 小时，n=150）、第三组（>6 小时，n=536）。结果显示，第一组患者的住院和 ICU 住院时间最短，住院死亡率最低（18.0%）；第三组患者的住院和 ICU 住院时间最长，住院死亡率最高（51.5%）。在生理指标方面，第三组患者的 APACHE II 评分和 SOFA 评分显著高于其他两组，提示其病情更为严重。第一组的机械通气时间最短，而 Group 3 最长，超声检查和去甲肾上腺素的使用率也在三组之间有所不同。住院时间和住院死亡率在各组间也有显著差异，第一组的住院死亡率显著低于其他两组。Kaplan-Meier 生存分析显示，延迟转移至 ICU 的患者在 28 天和 60 天的生存率显著低于及时转移的患者（log-rank P<0.001）。逻辑回归分析表明，延迟转移至 ICU 是住院死亡和 28 天死亡的独立预测因素（P<0.001）。限制性样条回归模型

进一步显示，随着转移时间延长，住院死亡风险呈非线性上升趋势。ROC 曲线分析显示，转移时间对预测住院死亡和 28 天死亡的效能较高（AUC 分别为 0.684 和 0.674）。

在分析早期使用超声（即在发生休克后 6 小时内）对休克患者预后的影响时，共有 251 例患者在休克发作 6 小时内接受了超声辅助诊疗。结果表明，早期使用超声与多项临床预后指标显著改善相关，包括：ICU 住院中位时间更短（4.23 [2.16; 8.72] 天 vs 5.13 [2.90; 9.00] 天），休克持续时间缩短（34.7 ± 26.2 小时 vs 39.9 ± 29.5 小时），ICU 转运时间提前（2.73 ± 9.12 小时 vs 5.49 ± 13.7 小时），住院死亡率降低（16.7% vs 24.6%），以及 ICU 28 天死亡率显著下降（13.9% vs 22.0%）（P<0.05）。Kaplan-Meier 生存曲线显示，早期超声干预组的 28 天生存率显著高于未使用超声组（log-rank P<0.05）。逻辑回归分析表明，早期使用超声是降低住院死亡率和 28 天死亡率的独立保护因素（P<0.05）。

此外，建立的休克患者院内死亡率预测模型表明，Apache II 评分、SOFA 评分、急性呼吸衰竭、重症肺炎、肾衰竭、INR、血乳酸、钠浓度、阴离子间隙、PaO_2和转移 ICU 时间为独立风险因素、而白蛋白、淋巴细胞计数、PaO_2/FiO_2 比值和 6 小时内的超声检查为保护因素。模型的 ROC、Hosmer-Lemeshow 检验、校准曲线和决策曲线均显示其具有良好的校准度和临床应用价值。

第二部分研究结果：本研究共纳入674名患者，排除因数据丢失的30名患者和失访的71名患者后，最终纳入540名患者。患者的平均值年龄为58±17岁，男性185名（34.26%），女性355名（65.74%）。患者类型包括急性呼吸和循环系统损害（68.15%）、多系统器官衰竭（30.19%）及术后监护（1.67%）。患者入组时的APACHE II评分平均值为19.95±8.38，SOFA评分平均值为7.10±2.52。根据OPACCUS执行率，将患者分为完全执行组（n=171）、中等执行组（n=149）和低执行组（n=220）。基线特征比较显示，完全执行组的 SOFA 平均值为 6.75 ± 2.43，明显低于其他组。中度执行组的SOFA平均值为（7.46±2.57），而低度执行组的平均 SOFA 最低，为（7.12±2.52）（F=3.19，P<0.05）。此外，因肾前性或休克情况导致尿量 <0.5 ml/kg·h 的患者比例在各组间存在显著差异

（$\chi^2 = 21.00$，$P < 0.001$）。其他指标未显示出统计学显著差异。完全执行组的30天病死率为21.05%，显著低于低执行组的36.82%（HR=1.646，95% CI: 1.082-2.505，P<0.05）。相较于中等执行组（28.86%），完全执行组的30天病死率也有所降低，但差异无统计学意义（HR=1.254，95% CI: 0.783-2.009，P>0.05）。在调整后的模型中，完全执行组的全因死亡率为21.05%，与低执行组的36.82%相比，差异有统计学意义（HR=1.646*, RMST=-3.223*）；而与中等执行组的28.86%相比，差异无统计学意义（HR=1.254, RMST=-3.783）。Kaplan-Meier分析显示，三组之间存在延迟效应，且曲线间有交叉，降低了Log-rank检验的效能。Fleming检验表明，30天内中段（P=0.0459）和后段（P=0.0399）三组间差异具有统计学意义。Landmark分析进一步表明，6天后，三组之间的生存率差异显著（Log-rank P=0.0253）。RMST分析显示，在30天内，高执行组的平均RMST最长，为19.774天，中等执行组为16.572天，低执行组为15.240天（P=0.039）。组间比较显示，低执行组的RMST显著低于完全执行组，差异为4.534天（P=0.043），进一步强调了较高OPACCUS执行率与改善生存结果之间的相关性。

微循环纠正时间：完全执行组的中位时间最短，但在30天死亡率的校正分析中无统计学意义（P>0.05）。

大循环纠正时间：三组间无显著差异（P=0.70）。

ICU费用和住院费用：完全执行组的ICU费用和住院费用显著低于中等执行组，分别少4.613万元（95%CI: 0.433-8.793）和5.583万元（95%CI: 0.963-10.202）（P<0.05）。

ICU住院天数和呼吸机使用天数：完全执行组的天数最短，但在30天死亡的单因素和多因素校正分析中，组间差异无统计学意义（P>0.05）。

结论：

本研究强调了早期转移至ICU对休克患者预后的重要性。第一部分的结果显示，延迟转移超过6小时显著增加了患者的死亡风险。因此，尽早识别并及时转

移休克患者对改善预后至关重要。此外，早期在休克管理中使用超声可以进一步提升患者预后。建立的院内死亡预测模型表现出较好的区分度和校准度，具有临床应用价值。该研究为制定优化的早期诊疗策略提供了实证支持，建议在临床实践中尽量缩短普通病房患者转入ICU的时间，并结合超声评估。

第二部分研究验证了基于可视化信息的OPACCUS方案在ICU中的应用效果。结果表明，OPACCUS方案显著提高了休克患者的存活率，缩短了ICU住院时间，并降低了住院费用。较高的OPACCUS执行率与更好的生存结果密切相关，这表明该方案在个性化休克管理中的有效性和广泛应用潜力。未来研究应进一步优化和推广该方案，以覆盖更广泛的患者群体，进一步提高休克管理的精准性和效率。

关键词：

休克；回顾性研究；转运策略；普通病房；预后；前瞻性研究；OPACCUS；可视化诊疗；重症超声；ICU 管理

Development and Validation of a Novel Shock Diagnosis and Treatment Protocol Based on Ultrasound Visual Information.

Abstract

Background:

Shock is one of the leading causes of death in critically ill patients, characterized by high morbidity and mortality rates. Globally, the overall mortality rate of shock can reach 30%-50%, with the main types being distributive shock, hypovolemic shock, cardiogenic shock, and obstructive shock. Each type of shock has different etiologies and requires distinct treatment strategies, making an individualized diagnostic and treatment pathway crucial for effective management. Early recognition and rapid intervention are essential for improving the prognosis of shock patients.

However, the management of shock in general wards faces several challenges. Limited equipment and resources, combined with the lack of real-time monitoring and standardized treatment protocols, result in delays in identifying and treating patients with shock. Patients diagnosed with shock in general wards often require urgent transfer to the ICU for specialized care. Despite this, there is no systematic research on how the timing of ICU transfer affects patient outcomes. The timing of transfer potentially influences the prognosis of shock patients, but clinical evidence to clarify this association remains lacking.

To address this gap, the first part of this study employs a retrospective cohort analysis to evaluate the impact of different transfer times on patient outcomes, providing a foundation for optimizing early diagnosis and treatment strategies for shock patients. Even within the ICU, rapidly and accurately identifying the type of shock and delivering personalized treatment remains a clinical challenge. While critical care ultrasound is widely used as a non-invasive bedside tool for assessing shock, there is currently no systematic protocol integrating this with other clinical data.

Therefore, this study proposes and validates the OPACCUS protocol, a

personalized shock assessment protocol based on critical care ultrasound. The OPACCUS protocol integrates etiological management, hemodynamic assessment, and physiological interventions to provide a more precise treatment pathway for shock patients.

Objective:

1. To systematically evaluate the impact of ICU transfer timing on the prognosis of shock patients in general wards, explore the value of early ultrasound-assisted diagnosis and treatment for shock, and identify key clinical and ultrasound indicators related to patient outcomes. Additionally, the study will analyze the relationship between suboptimal treatment practices in general wards and patient prognosis. This process will provide the theoretical foundation for the subsequent development and validation of a new ultrasound-based shock management protocol.

2. To develop and validate a personalized shock assessment protocol based on visual information (OPACCUS) that integrates critical care ultrasound and clinical data, establishing a diagnostic and treatment process centered on etiology management, refined hemodynamic therapy, and systemic response intervention to improve the management and treatment of shock patients.

3. To assess the clinical effectiveness of the OPACCUS protocol through multicenter studies, examining its impact on patient outcomes (such as mortality, length of stay, and costs) and validating its operability and effectiveness in complex clinical settings.

4. To promote the standardization and optimization of shock management protocols, providing specific clinical practice recommendations through the implementation and improvement of the OPACCUS protocol to enhance the precision and efficiency of shock management.

Materials and Methods:

The study is divided into two parts, aiming to systematically evaluate ICU transfer timing and the impact of ultrasound-guided diagnosis and treatment for the

prognosis of shock patients, focusing on core indicator selection and early treatment strategy optimization, as well as developing and validating the application of the OPACCUS protocol in shock management.

Part 1 is a retrospective cohort study that collected data from patients with shock transferred to the ICU at West China Hospital of Sichuan University between January 1, 2019, and January 31, 2024. Patients were categorized into three groups based on their transfer time from the general ward to the ICU: Group 1 (transfer time <3 hours), Group 2 (transfer time 3-6 hours), and Group 3 (transfer time >6 hours). These groupings were based on critical time windows for shock management, focusing on early (within 3 hours) and timely (within 6 hours) intervention strategies. We first compared the baseline characteristics of patients across these three groups. Kaplan-Meier survival curve analysis was used to assess the impact of different transfer times on in-hospital mortality, and survival differences between the groups were compared using log-rank tests. Additionally, logistic regression models were employed to examine the relationship between transfer time and in-hospital and 28-day mortality rates. The analysis also included restricted spline regression models and Receiver Operating Characteristic (ROC) curves to evaluate the efficacy of transfer time as a prognostic indicator. To evaluate the impact of early ultrasound use on in-hospital mortality in patients with shock, Kaplan-Meier survival curve analysis and logistic regression models were used to examine the association with in-hospital mortality and 28-day mortality. Finally, a predictive model for in-hospital mortality in shock patients was developed. Influencing factors were identified through univariate and multivariate logistic regression analyses, and the model's performance was assessed using ROC curves, the Hosmer-Lemeshow test, calibration curves, and decision curves.

Validation and Application of the Visualised OPACCUS Treatment Protocol

Background and Design of the OPACCUS Protocol: The first part of the retrospective analysis validated the importance of early transfer to the ICU and highlighted the necessity of developing a personalised shock treatment protocol based on visualised information (OPACCUS). The OPACCUS protocol is designed to integrate etiology management, hemodynamic assessment, and intervention of the

body's response to enable refined shock management. It was developed through multiple rounds of expert discussions, consensus-building, and continuous calibration.

Programme Development and Training: After establishing the OPACCUS protocol, the research team provided systematic training to ICU physicians across multiple centers to ensure they fully understood and could effectively implement the protocol. The execution process involves assessing the cause of shock, hemodynamics, and the body's response using critical care ultrasound and other clinical information. Based on these assessments, the OPACCUS protocol offers physicians a personalised treatment pathway.

Part 2 is a multicenter prospective observational cohort real-world study that included shock patients from ICUs in 20 hospitals in Southwest China between October 2022 and February 2024. The enrolled patients' basic information, traditional hemodynamic assessment indices, treatment methods, and treatment feedback were recorded and evaluated based on actual clinical needs. The use of the OPACCUS protocol was encouraged, but the specific application was at the attending physician's discretion. Patients were classified into three groups according to the OPACCUS execution rate: the full execution group (execution rate = 100%), the intermediate execution group (50% ≤ execution rate < 100%), and the low execution group (execution rate < 50%). The primary outcome measured was 30-day mortality; secondary outcomes included systemic circulatory correction time, microcirculatory correction time, time to improvement, ICU length of stay (LOS), hospital length of stay, ventilator days, ICU costs, and total hospital costs. Initially, baseline characteristics were compared across the three groups, followed by Kaplan-Meier survival curve analysis for 30-day mortality, with differences in 30-day mortality risk among the three groups assessed using Log-rank, Fleming, and Landmark tests. Further analyses were conducted using restricted mean survival time (RMST) regression for univariate and multivariate evaluations.

Results:

Part 1 of the study included 3,535 patients with shock who were transferred from

the general ward to the ICU, with a mean age of 56.4 ± 15.3 years; 65.5% (2,317) were male and 34.5% (1,218) were female. The average length of stay was 21.5 ± 21.7 days, with an ICU stay averaging 7.77 ± 13 days. The overall in-hospital mortality rate was 24.0%, and the average shock duration was 39.6 ± 29.3 hours. The distribution of shock types was as follows: distributive shock in 2,392 patients (67.7%), hypovolemic shock in 1,099 patients (31.1%), cardiogenic shock in 123 patients (3.48%), and obstructive shock in 98 patients (2.77%). Septic shock was the predominant subtype among distributive shocks (64.6%), while hemorrhagic shock constituted 15.0% of hypovolemic shocks. Patients were divided into three groups according to transfer time: Group 1 (<3 hours, n=2,849), Group 2 (3-6 hours, n=150), and Group 3 (>6 hours, n=536). The results showed that patients in Group 1 had the shortest hospital and ICU stays and the lowest in-hospital mortality rate (18.0%), while Group 3 had the longest hospital and ICU stays and the highest in-hospital mortality rate (51.5%). Physiological indicators such as APACHE II and SOFA scores were significantly higher in Group 3 compared to the other two groups, indicating a more severe condition in these patients. Group 1 had the shortest duration of mechanical ventilation, whereas Group 3 had the longest. The use of ultrasonography and norepinephrine also varied significantly among the groups. Overall, hospital stay duration and in-hospital mortality differed substantially between the groups, with Group 1 showing a significantly lower mortality rate than the other two groups. Kaplan-Meier survival analysis demonstrated that patients with delayed transfer to the ICU had significantly lower 28-day and 60-day survival rates compared to those who were transferred promptly (log-rank P<0.001). Logistic regression analysis indicated that delayed ICU transfer was an independent predictor of in-hospital and 28-day mortality (P<0.001). The restricted spline regression model further showed a non-linear increase in the risk of in-hospital death with prolonged transfer time. ROC curve analysis demonstrated that transfer time strongly predicted in-hospital and 28-day mortality (AUC of 0.684 and 0.674, respectively).

In analyzing the impact of early ultrasound use (within 6 hours of shock onset) on the prognosis of shock patients, 251 patients received ultrasound-assisted diagnosis

and treatment within 6 hours of shock onset. The results indicated that early ultrasound use was significantly associated with improvements in several clinical outcomes, including shorter median ICU stay (4.23 [2.16; 8.72] days vs. 5.13 [2.90; 9.00] days), reduced shock duration (34.7 ± 26.2 hours vs. 39.9 ± 29.5 hours), earlier ICU transfer (2.73 ± 9.12 hours vs. 5.49 ± 13.7 hours), lower in-hospital mortality (16.7% vs. 24.6%), and a significant reduction in 28-day ICU mortality (13.9% vs. 22.0%) ($P<0.05$). Kaplan-Meier survival curves showed that the 28-day survival rate in the early ultrasound group was significantly higher than in the non-ultrasound group (log-rank $P<0.05$). Logistic regression analysis further demonstrated that early ultrasound use was an independent protective factor for reducing in-hospital mortality and 28-day mortality ($P<0.05$).

In addition, the established in-hospital mortality prediction model for shock patients identified Apache II score, SOFA score, respiratory failure, pneumonia, kidney failure, INR, blood lactate levels, sodium concentration, anion gap, PaO_2, and delayed ICU transfer time as independent risk factors, while serum albumin levels, lymphocyte count, PaO_2/FiO_2 ratio, and ultrasound examination within 6 hours of shock onset were identified as protective factors. The model's ROC curve, Hosmer-Lemeshow test, calibration curve, and decision curve analysis all demonstrated good calibration and clinical applicability.

Part 2 of the study enrolled a total of 674 patients. After excluding 30 patients due to missing data and 71 patients lost to follow-up, 540 patients were included in the final analysis. The average age of the patients was 58±17 years, with 185 males (34.26%) and 355 females (65.74%). Patient types included acute respiratory and circulatory compromise (68.15%), multisystem organ failure (30.19%), and postoperative monitoring (1.67%). At enrollment, the mean APACHE II score was 19.95±8.38, and the mean SOFA score was 7.10±2.52. Based on the OPACCUS execution rate, patients were divided into a full execution group (n=171), an intermediate execution group (n=149), and a low execution group (n=220). Baseline characteristic comparisons showed that the mean SOFA in the full execute group was 6.75 ± 2.43, which was significantly lower than that of the other groups. The mean

value for the medium execute group was 7.46 ± 2.57, while the low execute group had the lowest mean SOFA at 7.12±2.52 (F=3.19, P<0.05). Additionally, there was a significant difference in the proportion of patients with urine volume <0.5 ml/kg.h due to prerenal or shock conditions among the groups (χ^2 = 21.00, P < 0.001). No other indicators showed statistically significant differences. The 30-day mortality rate in the full execution group was 21.05%, significantly lower than the 36.82% in the low execution group (HR=1.646, 95% CI: 1.082-2.505, P<0.05). Although the 30-day mortality rate was lower in the full execution group compared to the intermediate execution group (28.86%), the difference was not statistically significant (HR=1.254, 95% CI: 0.783-2.009, P>0.05). In the adjusted model, the all-cause mortality rate was 21.05% in the full execution group, a statistically significant difference compared to 36.82% in the low execution group (HR=1.646*, RMST=-3.223*), but not significantly different from the 28.86% in the intermediate execution group (HR=1.254, RMST=-3.783). Kaplan-Meier analysis indicated a delayed effect among the three groups, with crossover between the curves, reducing the efficacy of the Log-rank test. Fleming's test demonstrated statistically significant differences between the three groups in the mid (P=0.0459) and late (P=0.0399) segments within 30 days. Landmark analysis further showed a significant difference in survival rates between the groups after 6 days (Log-rank P=0.0253). RMST analysis revealed that within 30 days, the full execution group had the longest mean RMST at 19.774 days, compared to 16.572 days in the intermediate execution group and 15.240 days in the low execution group (P=0.039). Group comparisons showed a significantly shorter RMST in the low execution group than in the full execution group, with a difference of 4.534 days (P=0.043), highlighting the association between higher OPACCUS execution rates and improved survival outcomes. Microcirculatory Correction Time: The median time was the shortest in the full execution group, but this was not statistically significant in the adjusted analysis for 30-day mortality (P>0.05).

Systemic circulatory Correction Time: No significant differences were found between the three groups (P=0.70).

ICU and Hospital Costs: ICU and hospital costs were significantly lower in the

full execution group compared to the intermediate execution group, with reductions of ¥46,130 (95% CI: 0.433-8.793) and ¥55,830 (95% CI: 0.963-10.202) respectively ($P<0.05$).

ICU Length of Stay and Ventilator Days: Both were shortest in the full execution group; however, the differences were not statistically significant in the univariate and multivariate analyses adjusted for 30-day mortality ($P>0.05$).

Conclusion:

In summary, the first part of the study emphasizes the critical importance of minimizing transfer delays from the general ward to the ICU for patients in shock. Early ICU admission is associated with improved survival rates, better clinical indicators, and more efficient use of medical resources. Additionally, the early use of ultrasound in shock management might further enhance patient prognosis. The mortality prediction model demonstrated good discriminatory and calibration performance, indicating clinical utility. These findings provide compelling evidence to support the implementation of standardized protocols aimed at expediting ICU transfers and incorporating ultrasound assessments, thereby enhancing patient outcomes and advancing shock management practices in healthcare settings.

The second part of the study demonstrated that implementing the OPACCUS protocol in the ICU significantly improved the survival rates of patients with shock, reduced ICU length of stay, and lowered hospitalization costs. Higher OPACCUS implementation rates were associated with better survival outcomes. These findings underscore the effectiveness and potential of the OPACCUS protocol in shock management. Future research should aim to refine this protocol further to enhance outcomes across a broader patient population.

Key Words:

Shock; Retrospective Study; Transfer Strategy; General Ward; Prognosis; Prospective Study; OPACCUS; Visualization; Critical Care Ultrasound; ICU Management.

缩略词表

缩略词	英文全名	中文全名
A	Arterial Tension	动脉张力/动脉阻力
AG	Anion Gap	阴离子间隙
APACHE II	Acute Physiology and Chronic Health Evaluation II	急性生理和慢性病理健康状态评分系统 II
ALT	Alanine Aminotransferase	丙氨酸氨基转氨酶
AST	Aspartate Aminotransferase	门冬氨酸氨基转氨酶
AUC	Area Under the Curve	曲线下面积
BUN	Blood Urea Nitrogen	尿素氮
C	Systemic Congestion	静脉蓄积
CI	Confidence Interval	置信区间
CPR	Cardiopulmonary Resuscitation	心肺复苏术
CNY	Chinese Yuan	人民币
CO	Cardiac Output	心输出量
CPR	C-reactive protein	C-反应蛋白
Cr	Creatinine	血肌酐
CRRT	Continuous Renal Replacement Therapy	持续性肾脏替代治疗
CRT	Capillary Refill Time	毛细血管再充盈时间
DBP	Diastolic Blood Pressure	舒张压
DSMB	Data and Safety Monitoring Board	数据和安全监测委员会
ED	Emergency Department	急诊科
eGFR	Estimated Glomerular Filtration Rate	估算肾小球过滤率
ESCCM	European Society of Critical Care Medicine	欧洲重症医学学会
INR	International Normalized Ratio	国际化标准比值

缩略词	英文全名	中文全名
A	Arterial Tension	动脉张力/动脉阻力
ICU	Intensive Care Unit	重症监护病房
IQR	Interquartile Range	四分位数范围
GCS	Glasgow Coma Scale	格拉斯哥昏迷模型
HR	Heart rate	心率
KM	Kaplan-Meier Curve	卡普兰-迈耶曲线
IL-6	Interleukin-6	白细胞介素-6
Lac	Lactate	血乳酸
LOCF	Last Observation Carried Forward	
LOS	Length of Stay	住院时间
MAP	Mean Arterial Pressure	平均动脉压
MB	Creatine Kinase isoenzyme MB	肌酸激酶同工酶
MODS	Multiple Organ Dysfunction Syndrome	多器官功能障碍综合征
NE	Norepinephrine	去甲肾上腺素
O	Oxygen Metabolism	氧代谢
OR	Odds ratio	比值比
OI	Oxygenation index	氧合指数
P	Perfusion	灌注
PaO2	Arterial Oxygen Partial Pressure	动脉氧分压
PaCO2	Arterial Partial Pressure of Carbon Dioxide	动脉二氧化碳分压
PCT	Procalcitonin	降钙素原
PI	Perfusion Index	灌注指数
APTT	Activated Partial Thromboplastin Time	活化部分凝血活酶时间
RASS	Richmond Agitation-Sedation Scale	里士满激动镇静量评分
RBC	Red Blood Cell Count	红细胞计数

缩略词	英文全名	中文全名
A	Arterial Tension	动脉张力/动脉阻力
RCS	Restricted cubic spline	限制性样条回归模型
RMST	Restricted Mean Survival Time	受限平均存活时间回归
ROC	Receiver Operating Characteristic Curve	受试者工作特征曲线
RR	Respiration Rate	呼吸频率
S	Lesion search	病灶搜查
SBP	Systolic Blood Pressure	收缩压
SOFA	Sequential Organ Failure Assessment	序贯器官衰竭评分
ScvO2	Central Venous Oxygen Saturation	中心静脉氧饱和度
SpO2	Saturation of pulse Oxygen	血氧饱和度
T	Temperature	体温
TnT	Troponin T	肌钙蛋白 T
U	Unregulated Host Response	宿主不适反应
VIS	Vasoactive-Inotropic Score	血管活性药物评分
WBC	White blood Cell count	白细胞计数

Introduction

The concept of shock has undergone profound evolution over the past three centuries. Originally introduced by the French surgeon Le Dran in the 18th century, the term "shock" has been recognized for over 300 years as a critical medical condition with significant implications for patient survival and recovery [1, 2]. Throughout history, the understanding of shock has evolved from a simplistic notion of a sudden collapse to a complex physiological syndrome involving multiple organ systems. Despite remarkable advancements in medical science, shock remains one of the most severe and challenging conditions encountered in modern healthcare. It is characterized by a complex interplay of pathophysiological processes, diverse etiologies, and rapid progression, all of which continue to present substantial diagnostic and therapeutic challenges for clinicians[3-9].

In contemporary medical practice, the European Society of Critical Care Medicine (ESCCM) defines shock as a state of life-threatening acute circulatory failure, leading to impaired cellular oxygen utilization and delivery [10]. Within the intensive care unit (ICU) setting, shock is not only prevalent but also a critical issue, affecting approximately one-third of all ICU patients and significantly influencing morbidity and mortality rates [4, 11]. In the intensive care unit, shock is a prevalent and critical issue, affecting approximately one-third of all ICU patients[12]. Diagnosing shock requires a comprehensive assessment that integrates clinical presentation with hemodynamic measurements and biochemical markers. Key diagnostic criteria include systemic arterial hypotension, which reflects a significant drop in blood pressure; clinical signs of inadequate tissue perfusion, such as altered mental status, cool and clammy skin, and delayed capillary refill; and hyperlactatemia, indicating impaired tissue oxygenation and metabolism [13-15]. These indicators are essential for determining the severity of shock and for developing tailored treatment strategies aimed at stabilizing the patient's condition and improving overall outcomes.

Shock manifests in several distinct types, each with unique pathophysiological mechanisms and clinical presentations. The primary types of shock include hypovolemic shock, distributive shock, cardiogenic shock, and obstructive shock[16].

Among these, distributive shock, often resulting from sepsis, is particularly prevalent in ICUs and is a leading cause of ICU mortality. The different types of shock may be triggered by various factors such as severe blood loss, infection, myocardial infarction, or obstructive processes, which can lead to phases of ischemia, sludging of blood flow, and eventually exhaustive stages where cellular metabolism is severely compromised [17]. The clinical signs of shock often include manifestations of impaired microcirculation, such as cold and clammy skin, cyanosis of the extremities, and prolonged capillary refill, each signaling a need for urgent intervention.

Shock management involves a multi-faceted approach that addresses the underlying cause, stabilizes vital signs, ensures adequate microcirculatory perfusion to critical organs, and improves cellular metabolism. Therapeutic strategies include fluid resuscitation, the administration of vasoactive drugs, and cause-specific treatments such as antibiotic therapy for septic shock, blood transfusions for hemorrhagic shock, and thrombolytic therapy for obstructive shock [18]. Each therapeutic intervention is tailored to the specific type and severity of shock, aiming to restore hemodynamic stability and optimize tissue oxygenation.

The incidence of shock in intensive care units is notably high. Statistics indicate that approximately 35% of ICU patients in medium and large hospitals in North America experience some form of shock, with mortality rates often exceeding 50% [19]. In the United States alone, over 1.2 million patients are admitted to emergency departments annually with shock, resulting in billions of dollars in associated medical costs [20]. The financial burden of shock, estimated to exceed $1 billion annually, underscores the need for effective management strategies to reduce costs and improve outcomes.

Shock often develops rapidly and insidiously, with few obvious early signs, making timely diagnosis and intervention critical. Research indicates that in patients with septic shock, each hour of delay in initiating resuscitation is associated with an approximately 8% increase in mortality [21, 22]. This statistic highlights the importance of prompt intervention and real-time monitoring, which are crucial for reducing morbidity and mortality and alleviating the healthcare burden associated with shock.

Continuous monitoring of hemodynamic parameters is vital for the effective management of shock. Hemodynamic indicators, such as blood pressure, circulating blood volume, and cardiac output, are essential for assessing the severity of shock and guiding therapeutic decisions [10, 23]. The need for high-performance, non-invasive monitoring technologies is evident, as these tools facilitate the monitoring of key indicators across various healthcare settings, from emergency departments to general wards and ICUs [24]. In cases of refractory shock, where initial interventions fail to stabilize the patient, there is a high risk of progression to systemic organ failure and other life-threatening complications [25, 26]. Thus, early and aggressive intervention is particularly important for high-risk patients, including those with hemorrhage, severe infections, and extensive burns [27]. The concept of the "Golden Hours" underscores this urgency; early interventions such as lactate monitoring, fluid resuscitation, and the empiric use of antibiotics and vasoactive medications are critical to improve outcomes for patients in shock.

However, the management of shock in general wards presents unique challenges. These settings often lack advanced medical equipment and resources, such as mechanical ventilation, vasoactive drug infusions, and sophisticated hemodynamic monitoring systems like the PICCO or ECMO, which are typically available in ICUs [28]. Furthermore, medical staff in general wards may have limited experience in recognizing and managing shock, and there may be a lack of systematic guidelines to guide treatment. When patients with shock are identified in general wards, they usually require rapid transfer to the ICU for more specialized and comprehensive care. The ICU provides an environment equipped to support earlier interventions, including precise hemodynamic monitoring and advanced therapies, which are crucial for improving patient survival and prognosis [29].

The timely transfer of patients with shock from general wards to the ICU is critical, yet the impact of delays in this process remains under-explored. Some studies have indicated that delays in emergency department (ED) to ICU transfers are associated with increased mortality and prolonged ventilation times in patients with respiratory failure [30-32]. However, other studies have not confirmed this association,

suggesting that the relationship between transfer times and outcomes may be more complex and dependent on various factors, including the patient's initial condition and the quality of care provided before ICU admission [33, 34].

Despite the high prevalence of shock in the ICU, there is limited information on the correlation between the duration and treatment of shock prior to ICU admission and the prognosis of patients with shock[35]. A significant knowledge gap exists regarding the early predictors of shock outcomes in critically ill patients, particularly concerning the impact of sustained shock in the general ward and the timing of transfer to the ICU.

Therefore, this Part 1 study aims to address this gap by analyzing the relationship between the duration of shock before transferring patients from the general ward to the ICU, the therapeutic measures taken, and the duration and prognosis of shock after ICU admission, through a retrospective cohort study. This study will explore the impact of early intervention on patient prognosis and develop predictive models to improve the management of shock in critically ill patients. By doing so, it aims to provide more effective diagnostic and therapeutic strategies in clinical practice, ultimately enhancing patient outcomes and reducing the overall burden of shock on healthcare systems.

Recent studies have delved deeper into the pathophysiological mechanisms underlying shock, revealing that an excessive systemic inflammatory response can precipitate a cascade of detrimental events. This includes widespread microcirculatory injury, pulmonary edema, and organ microcirculatory dysfunction. Such disruptions not only prolong the duration of shock but also intensify the severity of the patient's condition, thereby significantly influencing their prognosis. The microcirculatory disturbances affect nutrient and oxygen delivery at the cellular level, leading to organ failure and, ultimately, death if not rapidly and effectively managed[36-38]. Therefore, in managing patients with shock, it is imperative to closely monitor the systemic inflammatory response and develop novel therapeutic strategies that can modulate this response to improve patient outcomes.

In the ICU, the primary challenges in treating shock involve the rapid and

accurate identification of the type of shock, timely and continuous hemodynamic monitoring, and effective management of the underlying causes of shock, alongside controlling the body's excessive inflammatory and stress responses. The ICU setting provides a significant advantage due to its access to advanced technology and standardized treatment protocols, which are crucial in managing complex and rapidly evolving clinical conditions like shock. The ICU is equipped with comprehensive monitoring and therapeutic devices, including ECMO, PICCO systems, ventilators, dialysis machines, and sophisticated hemodynamic monitoring tools. These devices are essential for providing real-time data on a patient's cardiovascular status, respiratory function, and metabolic needs, allowing for immediate and precise interventions that can stabilize critically ill patients[39, 40]. Furthermore, ICU teams are composed of multidisciplinary experts who continuously update their knowledge and skills through regular training sessions and active participation in international research projects. This ongoing professional development ensures that the ICU team is well-versed in the latest therapeutic techniques and research findings, enabling them to formulate and implement optimized treatment protocols and guidelines. Such efforts are vital for ensuring that patients receive the highest standard of care, thereby improving their chances of survival and recovery. In contrast, general wards often lack the necessary resources, advanced equipment, and specialized personnel to provide the same level of comprehensive and timely monitoring and treatment as ICUs. This discrepancy can lead to the deterioration of shock patients' conditions and missed opportunities for timely interventions that could potentially alter their outcomes.

To identify key indicators associated with shock prognosis, a retrospective cohort study was conducted. The data obtained from this study serves as the foundation for developing a new diagnostic and therapeutic protocol aimed at improving patient outcomes in shock management. To address the multifaceted challenges of managing shock, ICU treatment strategies have evolved into a comprehensive "three-pronged" approach that integrates etiology management, targeted hemodynamic therapy, and systemic response intervention. Etiology management involves targeting the root causes of shock, such as administering anti-infective therapies for septic shock,

controlling hemorrhage in hypovolemic shock, or relieving mechanical obstructions in obstructive shock. These interventions are fundamental to stabilizing patients and are often the first steps in shock management[41, 42]. Precise hemodynamic therapy focuses on restoring adequate tissue perfusion and achieving a balance between oxygen supply and demand. This is accomplished through precise hemodynamic monitoring and targeted therapeutic interventions, including the use of vasoactive drugs to support blood pressure, mechanical ventilation to improve oxygenation, and blood purification techniques to remove inflammatory mediators from the circulation. Systemic response intervention aims to modulate the excessive systemic inflammatory response that often accompanies shock. This can be achieved by administering immunomodulators, corticosteroids, and other anti-inflammatory agents to reduce the risk of additional organ damage caused by the body's own immune response[43-46]. Together, these three components form a comprehensive and integrated shock management framework that addresses the complex and dynamic nature of shock.

Critical care ultrasound has emerged as a pivotal tool in the ICU for the diagnosis, differentiation, management, and assessment of shock. This non-invasive imaging modality allows for real-time visualization of cardiac function, hemodynamic status, and lung conditions, providing essential information that helps clinicians quickly differentiate between various types of shock, such as cardiogenic, hypovolemic, obstructive, and distributive shock[47-50]. Common ultrasound assessments in the ICU include echocardiography (to evaluate cardiac structure and function), vascular ultrasound (to assess blood flow dynamics), and lung ultrasound (to detect pulmonary edema and pleural effusion)[51-53]. These assessments are invaluable not only for guiding fluid resuscitation and optimizing the use of vasoactive drugs but also for identifying potential life-threatening conditions such as pericardial tamponade or pulmonary embolism. By providing critical prognostic information, ultrasound supports informed clinical decision-making, allowing for timely and appropriate therapeutic interventions.

In managing shock, ultrasound assessment has demonstrated unique advantages in evaluating various aspects of cardiovascular health, including cardiac function,

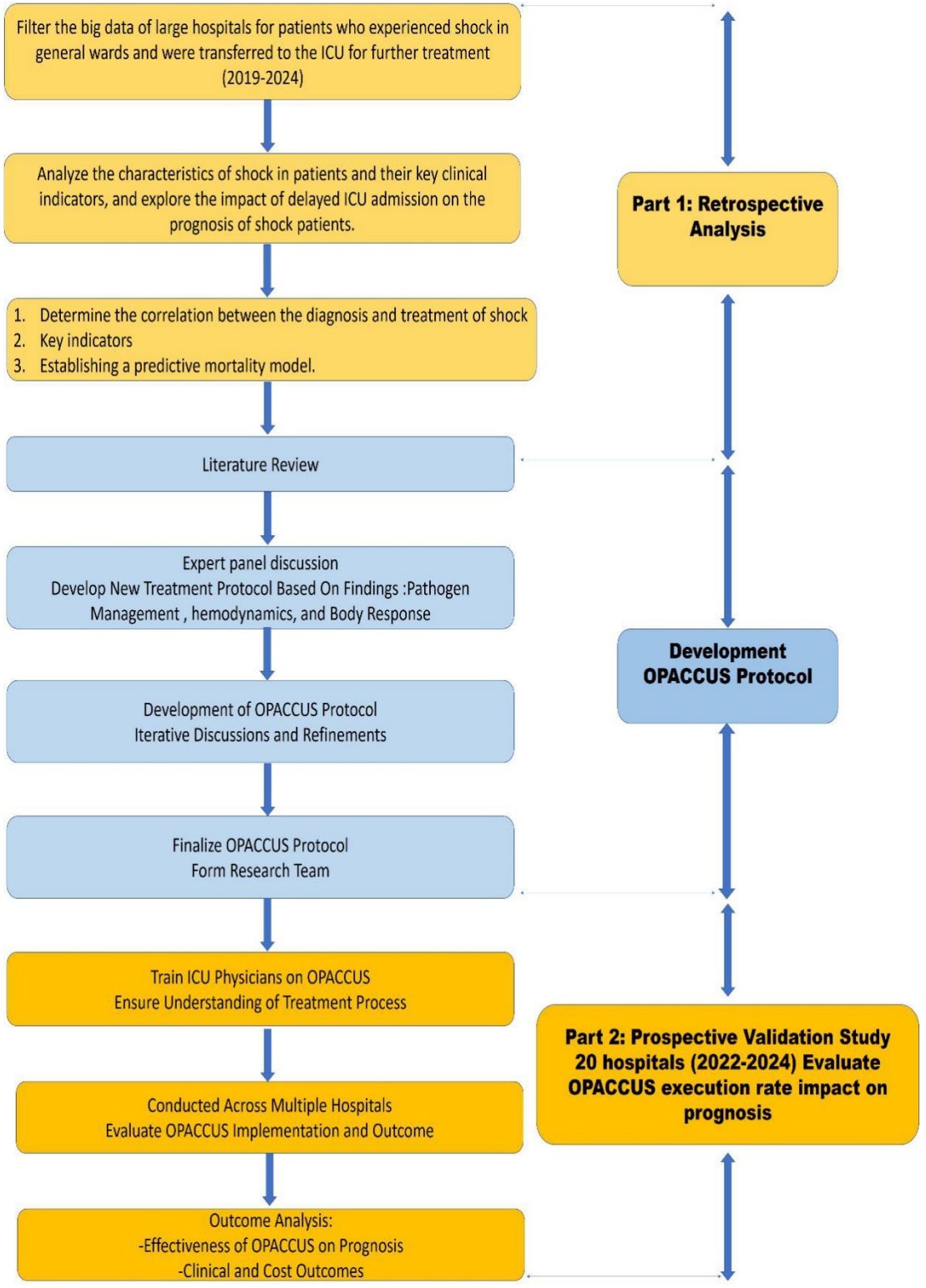
organ perfusion, and vascular tone[47, 54-57]. The 2014 European Society of Intensive Care Medicine guidelines advocate for the use of echocardiography as the preferred method for the initial assessment of shock type due to its ability to provide comprehensive insights into cardiac performance and fluid status[10]. However, despite its widespread use and recognized value, there is still no universally accepted, standardized protocol for the application of ultrasound in shock management across different ICUs and patient populations.[4]. Additionally, the 2016 International Federation for Emergency Medicine's consensus guidelines on the use of bedside ultrasound for unexplained hypotension and cardiac arrest provide only a general overview of managing hypotension, lacking specific directives for diverse shock scenarios[43]. While some studies, such as those by Kanji et al., have demonstrated the potential of echocardiography to reduce mortality in shock patients, these findings underscore the need for more structured research to systematically validate the effectiveness of ultrasound-guided shock management strategies[58]. Despite these studies highlighting the role of critical care ultrasound in shock assessment, there remains a lack of a standardized process that integrates assessment and analysis to systematically validate the relationship between shock management and prognosis. The OPACCUS protocol addresses this gap by standardizing ultrasound-based assessments into a comprehensive visualized diagnostic and therapeutic pathway, specifically designed for shock management.

Current critical care ultrasound protocols for shock often emphasize cardiac and volume assessment while overlooking other critical aspects of hemodynamics, such as systemic vascular resistance, microcirculatory function, and the body's broader inflammatory response. There is also a lack of research focusing on how these factors impact patient prognosis. In practice, the effective application of critical care ultrasound requires that physicians not only acquire accurate images but also possess the ability to interpret these images correctly within the broader context of the patient's clinical condition. This level of expertise is necessary to make precise assessments and guide clinical management decisions effectively[59, 60]. Therefore, a well-structured diagnostic and therapeutic process is crucial. It can help critical care physicians

systematically gather ultrasound data and analyze patient conditions in a standardized manner, thereby enhancing the quality of ultrasound use and improving diagnostic and therapeutic efficiency.

To address these gaps and improve shock management, we have integrated critical care ultrasound visualization techniques into three key areas of shock management: etiology management (etiology), refined hemodynamic therapy (hemodynamic), and systemic response intervention (systemic response). Building on this comprehensive framework, we have developed a novel visual shock assessment protocol termed OPACCUS. This protocol incorporates detailed evaluations of various cardiac output determinants, including right and left ventricular function, pericardium, valvular structures, outflow tracts, and intravascular volume status. It also emphasizes the assessment of tissue and organ microcirculatory oxygen metabolism, perfusion, antegrade arterial flow, and retrograde venous return. By providing a holistic view of the patient's hemodynamic status and integrating this information into clinical decision-making, the OPACCUS protocol aims to enhance patient outcomes. This study seeks to explore the impact of implementing the OPACCUS assessment protocol on patient outcomes through a multicenter real-world cohort study, thereby contributing to the advancement of shock management in the ICU setting.

Flowchart of the study design



Materials And Methods

This study is divided into two parts: the first part is a retrospective cohort study aimed at evaluating ICU transfer timing and the impact of ultrasound-guided diagnosis and treatment on shock patients, focusing on core indicator selection and early treatment strategy optimization. The second part is a prospective real-world study evaluating the effect of a new visual shock management protocol (OPACCUS), which integrates etiology, hemodynamics, and systemic response, on patient prognosis. In the first part, we selected 28-day mortality as the primary outcome measure, as it better captures the short-term effects of transfer delays on prognosis. For the second part, we used 30-day mortality as the primary outcome to assess longer-term mortality risks, allowing for a comprehensive evaluation of the OPACCUS protocol's effectiveness.

1. Evaluation of ICU Transfer Timing and Ultrasound-Guided Diagnosis and Treatment for the Prognosis of Shock Patients: Core Indicator Selection and Early Strategy Enhancement

1.1 Research Design and Ethical Approval

This study was designed as a single-center retrospective cohort analysis aimed at evaluating the prognostic impact of delays in transferring patients who developed shock from the general ward to the ICU. The study was conducted at West China Hospital of Sichuan University, a leading tertiary care institution known for its advanced critical care services. A comprehensive review of electronic medical records was carried out, covering a period from January 1, 2019, at 00:00 hours to January 31, 2024, at 23:59 hours. The study adhered strictly to the ethical principles outlined in the Declaration of Helsinki to ensure the protection of patient rights and ethical standards in medical research. Ethical approval for this study was granted by the Ethics Committee of West China Hospital of Sichuan University under Ethics Review No. 2022 (990). Given the retrospective nature of this research, the requirement for obtaining patient informed consent was waived by the ethics committee. To maintain patient confidentiality and privacy, all data were anonymized, and stringent data protection and privacy regulations were followed to ensure that all patient information

was handled securely and with the highest level of care.

1.2 Study Population and Inclusion Criteria

1.2.1 Study Population:

The study population consisted of patients who developed shock while in the general ward and were subsequently transferred to the ICU at West China Hospital of Sichuan University between January 1, 2019, and January 31, 2024. These patients were included based on their clinical diagnosis of shock and the necessity for specialized ICU care due to their critical condition.

1.2.2 Inclusion Criteria:

To be included in the study, patients had to meet the following criteria:

1) **First-time ICU Transfer:** The patient must have been transferred to the ICU for the first time from the general ward during the study period.

2) **Clinical Diagnosis of Shock:** Patients needed to meet at least two of the following diagnostic criteria for shock:

- **Blood Pressure Criteria:** systolic blood pressure < 90 mmHg or mean arterial pressure (MAP) < 65 mmHg, or > 40 mmHg drop from baseline blood pressure;
- **Vasoactive Medications:** vasoactive medications are required to maintain blood pressure (e.g., posterior pituitary, norepinephrine, dopamine, dobutamine, epinephrine, mesalamine, etc.);
- **Tissue Hypoperfusion Manifestations:** at least one of the following three manifestations:

(1) Urine output < 0.5 mL/kg/h for more than 1 hour;

(2) Altered mental status, such as apathy and stupor;

(3) Blood lactate level > 2 mmol/L.

3) **Persistent State of Shock Post-ICU Transfer:** Patients had to continue demonstrating signs of shock after ICU transfer, evidenced by the ongoing need for vasoactive medications, sustained low blood pressure (below 90/60 mmHg), or continued manifestations of tissue hypoperfusion.

1.2.3 Exclusion criteria:

Patients were excluded from the study if they met any of the following conditions:

1) **Age:** Patients aged ≤ 18 years.;

2) **Incomplete Data:** Patients with incomplete data necessary for scoring or incomplete hospital information.

3) **Direct ICU Transfer:** Patients are transferred directly to the ICU from outpatient or emergency settings.

4) **Postoperative Transfers:** Patients transferred to the ICU directly from the operating room post-surgery.

5) **Malignant Tumors:** Patients diagnosed with malignant tumors.

6) **Pregnancy and Lactation:** Pregnant or lactating patients.

1.3 Definition and Classification of Shock

Definition of Shock Onset:

In this study, shock onset is defined as the acute occurrence of hypotension in patients while in the general ward, characterized by a sustained systolic blood pressure below 90 mmHg or MAP below 65 mmHg, along with clinical signs of inadequate tissue perfusion, such as altered mental status, oliguria, or elevated blood lactate levels. The exact timing of shock onset was determined retrospectively by reviewing ward records for the first instance of qualifying hypotension and tissue hypoperfusion. The initiation of vasoactive medications (e.g., norepinephrine, epinephrine, vasopressin, etc.) to maintain blood pressure was also considered as an indicator of shock onset.

Classification of Shock Types:

Based on standard clinical classification, this study categorized shock into the following five types:

1) Septic Shock:

Defined as shock caused by infection, with patients requiring vasoactive medications to maintain MAP ⩾65 mmHg despite adequate fluid resuscitation. Additional criteria for septic shock include an elevated Sequential Organ Failure Assessment (SOFA) score, and a blood lactate level greater than 2 mmol/L. The diagnosis of septic shock requires the presence of infection along with both hemodynamic instability (necessitating vasoactive support) and metabolic derangement (lactate > 2 mmol/L).

2) Cardiogenic Shock:

Cardiogenic shock occurs due to severe impairment of cardiac pump function, leading to a significant reduction in cardiac output that fails to meet the body's metabolic demands. Diagnostic criteria include persistent hypotension (SBP <90 mmHg or MAP <60 mmHg, or a drop of >30 mmHg from baseline), despite adequate fluid resuscitation, with evidence of hypoperfusion. Patients may present with decreased urine output (<30 mL/h or <0.5 mL/kg/h), elevated lactate levels (>2 mmol/L), and altered mental status. Ultrasound (e.g., echocardiography) or other imaging modalities typically reveal severe impairment of cardiac contractile function, such as elevated CVP or pulmonary capillary wedge pressure > 15 mmHg. Treatment may involve inotropic agents (e.g., norepinephrine, epinephrine, dobutamine) and, in severe cases, mechanical circulatory support (e.g., intra-aortic balloon pump [IABP], extracorporeal membrane oxygenation [ECMO]) to stabilize hemodynamics.

3) Hypovolemic Shock:

Hypovolemic shock results from significant blood or fluid loss, leading to decreased circulating blood volume and inadequate tissue perfusion. Ultrasound typically reveals a collapsed or narrow inferior vena cava (IVC), indicating low intravascular volume. Clinically, patients present with low CVP), tachycardia, hypotension, and signs of poor organ perfusion. Symptoms generally improve after adequate fluid resuscitation, which restores vascular volume and stabilizes blood pressure.

4) Distributive Shock:

Often seen in sepsis, this type of shock is characterized by systemic vasodilation, leading to a redistribution of blood flow and severe hypotension.

5) Obstructive Shock:

Shock is caused by mechanical obstruction to blood flow, commonly seen in conditions such as massive pulmonary embolism, tension pneumothorax, or cardiac tamponade. Obstructive shock is characterized by hypotension due to impeded blood flow, despite normal cardiac function. Treatment usually involves addressing the source of the obstruction (e.g., thoracic drainage for pneumothorax or thrombolysis for embolism).

The classification of shock types was determined based on clinical presentation, laboratory findings, and the requirement for vasopressor support. This classification was verified at the time of ICU transfer by thoroughly reviewing patient records and diagnostic data from the hospital's information system (HIS).

1.4 Data collection:

Data were collected by querying the database of the information center of West China Hospital of Sichuan University and the Hospital Information System (HIS) for electronic medical records to obtain clinical information for patient inclusion in the study. The specific data collected included:

1) **General Patient Admission Information:** Age, gender, ethnicity, marital status, current medical history, past history, and diagnosis.

2) **Vital Signs:** Temperature (T), respiration rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and oxygen saturation (SpO2).

3) **Bedside Arterial Blood Gas Analysis Results:** Arterial partial pressure of oxygen (PaO2), arterial partial pressure of carbon dioxide (PaCO2), oxygenation index (OI), sodium (Na), potassium (K), calcium (Ca), glucose (Glu), and lactate levels.

4) **Laboratory Test Results:** Red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), liver enzymes (AST, ALT), coagulation parameters (PT, INR), hemoglobin, serum creatinine, blood urea nitrogen (BUN), creatine kinase isoenzyme MB (CK-MB), troponin T (TnT), and C-reactive protein (CRP).

5) **Severity Scores:** APACHE II score, SOFA score, and Glasgow Coma Scale calculated at shock onset and on the first ICU day (detailed in supplementary tables).

6) **Treatment Information:** Duration of mechanical ventilation, use of ultrasound, antibiotics, and vasoactive medications (e.g., norepinephrine, epinephrine), and hourly urine output.

7) **Time-related Variables:** Length of hospitalization, ICU stay duration, in-hospital mortality, 28-day morbidity and mortality rates, time from shock onset to ICU transfer, total shock duration, and ICU transfer timing relative to work hours (defined as work hours: Monday-Friday, 7:00 a.m. to 10:59 p.m.; off-hours: Monday-Friday,

11:00 p.m. to 6:59 a.m., and weekends).

1.5 Research Groups

In this study, patients were classified into three distinct groups based on the timing of their transfer to the ICU following the onset of shock (pre-ICU shock time). Group 1 includes patients transferred to the ICU within less than 3 hours of shock onset. Group 2 encompasses those transferred within a window of 3 to 6 hours, while Group 3 comprises patients whose transfer occurred after more than 6 hours. This categorization reflects critical time thresholds for early intervention, emphasizing the significance of timely shock management. Specifically, interventions conducted within the initial 6 hours and management within the first 3 hours are pivotal for optimizing patient outcomes.

1.5 Quality Control Data

To control for potential confounding due to baseline disease severity, we meticulously collected detailed data on all relevant clinical indicators at the onset of shock. This included comprehensive severity scores and laboratory values, which allowed us to adjust for these variables in our statistical analysis.

Before data collection, the study's objectives and research design were thoroughly reviewed and refined in consultation with the supervisor and a panel of subject matter experts. This collaborative approach ensured the formulation of a scientifically rigorous protocol.

To maintain consistency and accuracy, a unified training program was conducted for all personnel involved in data collection. Study indicators were systematically recorded using a standardized patient data collection form. Adherence to predefined inclusion and exclusion criteria was strictly observed throughout the data collection process.

Data accuracy was further ensured through a rigorous verification process. Any significant discrepancies in test or examination results were promptly addressed by consulting with the primary or associate physician at the Department of Critical Care, West China Hospital of Sichuan University. This collaborative review aimed to confirm the validity and reliability of the data, ensuring that the findings of the study

are both accurate and dependable.

2. Prognostic Impact of a New Visualized OPACCUS Diagnostic and Therapeutic Assessment Process for Shock Based on Etiology, hemodynamics, and Organism Response

2.1 Study Design and Supervision

The second part of this study was a prospective, multicenter, real-world study designed to evaluate the effectiveness of the OPACCUS assessment protocol in managing patients with shock. This study was conducted from October 2022 to February 2024 in the ICUs of 20 hospitals in Southwest China. The study design was a multicenter, prospective observational cohort real-world study registered under the number **ChiCTR2200061952.** The study protocol received approval from the Ethics Committee of West China Hospital of Sichuan University, with Ethics Approval No. **(990) 2022**.

To ensure the scientific validity and accuracy of the data, a Data and Safety Monitoring Board (DSMB) was established[61, 62]. The DSMB was responsible for overseeing the entire study process, including reviewing the completeness and accuracy of data and monitoring patient safety. The steering committee provided comprehensive planning during the trial design phase and was tasked with ensuring that all participating centers strictly adhered to the study protocol, thereby ensuring the reliability of the study results.

The research team also held regular meetings to review the study's progress, address any issues encountered during implementation, and make necessary adjustments to the study protocol as needed. The participating centers entered all data into a unified data management platform to ensure standardization and consistency. An independent data analysis team conducted data management and analysis to ensure objectivity and the accuracy of the analysis results.

This prospective multicenter real-world study's design, implementation, and oversight were rigorously reviewed and controlled to ensure the study adhered to the highest standards of scientific rigour, ethics, and clinical practice.

2.2 Inclusion and Exclusion Criteria

This study included adult shock patients (aged >18 years) from the ICUs of 20 hospitals in Southwest China who were admitted between October 2022 and February 2024. The specific inclusion and exclusion criteria were as follows:

2.2.1 Inclusion Criteria:

1) Patients admitted to the ICU;

2) Meeting the **diagnostic criteria for shock**, including:

- Hypotension (systolic blood pressure [SBP] <90 mmHg, mean arterial pressure [MAP] <70 mmHg, a drop in SBP of more than 40 mmHg from normal, or 2 standard deviations below normal values), with other causes of hypotension excluded;
- Or, while maintained on vasopressor medications, showing signs of tissue hypoperfusion. Manifestations of tissue hypoperfusion include any of the following: urine output <0.5 ml/kg/h for more than 1 hour, altered mental status, mottled skin, or a blood lactate level greater than 2 mmol/L;

3) **Clinical judgment:** If any of the above criteria were met, and the patient's attending physician clinically determined that the patient was in shock.

All patients meeting the inclusion criteria were required to provide informed consent signed by an authorized representative before participating in the study, ensuring that the patient or their proxy fully understood the study's purpose, methodology, and potential risks.

2.2.2 Exclusion Criteria:

1) Age < 18 years;

2) Pregnancy;

3) Refusal to participate in the study by either the supervising physician or the patient and their family;

4) Brain death;

5) An estimated life expectancy of less than 24 hours as assessed by the attending physician;

6) End-stage malignant tumors.

2.3 OPACCUS Assessment Program and Platform Construction

The OPACCUS assessment program was developed by a team of experienced experts, utilizing a trinity thinking model that focuses on etiologies, hemodynamics, and organism response to systematically manage patients with shock. The program comprises the following three main components:

1) Determination of Etiology:

Identify the primary cause of shock, such as infection, hemorrhage, trauma, obstruction, or myocardial damage.

2) Classification of Dysregulated Body Response:

Assess the types of dysregulated organismal responses, including autonomic dysfunction due to excessive stress, immune-inflammatory response dysregulation caused by inflammatory storms, coagulation abnormalities resulting from hypercoagulability or thrombosis, and bioenergetic imbalance due to mitochondrial dysfunction at the cellular level.

3) Phenotypic Assessment of Hemodynamic Disorders:

Identify phenotypes of hemodynamic disturbances, such as alterations in vascular tone, resistance, cardiac output (CO), and venous stasis.

Assessment Frequency:

- **Resuscitation Period:** Assess every 1-3 hours.
- **Optimization Phase:** Assess every 4-6 hours.
- **Stabilization Phase:** Assess every 12-24 hours.

Critical Care Ultrasound:

Ultrasound technology plays a crucial role in the OPACCUS assessment program due to its non-invasive and efficient capabilities. It provides essential information at every stage of the model, including identifying underlying conditions, primary lesions, organismal response manifestations, and the corresponding blood gas exchange function phenotypes of hemodynamic disturbances. Additionally, the Critical Care Hemodynamic Therapy Collaborative Group and the Critical Care Ultrasound Visualization Research Group have developed a visual, refined, and modular fusion monitoring system based on critical care ultrasound, which has refined and established the concept of ultrasound hemodynamics. By integrating critical care ultrasound into

diagnostic and therapeutic protocols and simultaneously monitoring systemic circulation, microcirculation, oxygen metabolism, primary pathology, and excessive organismal responses, the OPACCUS diagnostic and therapeutic protocol is established. This protocol focuses on etiological screening and treatment, blocking excessive organismal responses, and fine-tuning hemodynamic management to correct pathophysiological changes from oxygen supply and demand to perfusion and system circulation, effectively treating patients with a holistic approach from end to beginning.

Training and Implementation: Based on the construction of the OPACCUS diagnostic protocol, systematic training, and case demonstrations will be provided to all participating study medical staff who have foundational knowledge in critical care ultrasound. Each participating centre must conduct shock patient assessments according to the new OPACCUS protocol, helping intensivists better understand the condition of shock patients, the mechanisms involved, and the priorities for treatment.

Information Design Platform Development:

An information design platform has been developed to capture the following data:

- **Basic Patient Information:** Including demographics, disease history, and laboratory test results.
- **Shock Hemodynamic Indicators:** Vital signs and measurements relevant to shock management.
- **Critical Care Ultrasound Visualization Information:** Including cardiac structure and function, vena cava volume and variations, pulmonary artery status, vascular tone, pulmonary compliance, lesion morphology, and manifestations of stress cardiomyopathy.
- **Execution of the OPACCUS Diagnostic and Treatment Protocol:** Documentation of how the protocol is applied in each case.
- **Patient Outcome Information:** Data on patient progress and outcomes to evaluate the effectiveness of the protocol.

2.4 Study Protocol

Once patients are enrolled in the study, their basic information, traditional hemodynamic assessment parameters related to shock, treatment modalities, and

feedback on treatments will be recorded and evaluated based on actual clinical needs. The decision to apply the OPACCUS assessment protocol is determined by the clinical assessment of the patient's attending physician:

- **Application of the OPACCUS Assessment Protocol:** The complete OPACCUS assessment is performed, and the results are provided to the patient's attending physician. The attending physician then selects an appropriate treatment plan based on the assessment results and implements the treatment without any additional intervention from the study team.
- **Non-Programmed Assessment:** If the attending physician only uses critical care ultrasound for a non-programmed assessment, this will be considered as not having performed the OPACCUS programmed assessment.

The investigator will objectively record the feedback on treatment modalities and review the outcome indicators. A patient will be considered to have fully corrected shock if their lactate levels are normal, blood pressure is restored to normal (without the use of vasoactive medications), and urine output is normal (excluding cases of impaired renal function). Once these criteria are met, the patient will be discharged from the study, prognostic indicators will be recorded, and the patient will be followed up accordingly.

OPACCUS Execution Rate:

The OPACCUS execution rate is defined as the proportion of actually completed OPACCUS assessments to the total number of planned assessments (OPACCUS execution rate = number of OPACCUS assessments completed per patient / total number of planned assessments × 100%).

2.5 Schematic of the Detailed OPACCUS Programme

This section will provide a visual representation of the detailed steps and processes involved in the OPACCUS assessment program.

Table 1: Detailed Description and Reference Values of Each Scoring Indicator in the OPACCUS Assessment.

Key Element		Central Issues	Criterion	Therapeutic Options
HEMODYNAMICS	**Oxygen Metabolism (O)**	1.1. Is there evidence of excessive oxygen consumption?	**Basis 1:** Metabolic enhancement: pain, anxiety, endocrine factors (e.g., hyperthyroidism); fever, chills, stress, etc. **Basis 2:** Increased work: ultrasound findings of high respiratory drive; ultrasound findings of high circulatory drive.	Analgesia/sedation/anti-sympathetic therapy/muscle relaxation/temperature control
		1.2. Is there insufficient oxygen supply?	**Basis 1:** ScvO2 decreases under controlled oxygen consumption; ScvO2 is "too low" with uncontrolled oxygen consumption. **Basis 2:** Elevated lactate (lac) under controlled oxygen consumption (note: issues with oxygen distribution and utilization are analyzed as part of exclusion criteria).	Further assessment
	Perfusion (P)	2. Is there tissue hypoperfusion? (Hypoperfusion-related oxygen deficiency)	**Basis 1:** Decreased perfusion index (PI) (<0.9s) **Basis 2:** Prolonged capillary refill time (CRT) (3s) and/or mottling	Further assessment
	Arterial Tension (A)	3. Is there any pre-obstruction? (Endogenous hypotension vs. iatrogenic high resistance)	**Basis 1:** Vasoconstrictor drugs maintain blood pressure, but perfusion remains inadequate. **Basis 2:** The resistance index of the snuffbox is significantly increased. **Basis 3:** The blood flow spectrum of the snuffbox shows small sharp waves and T-waves (narrow base and small area under the curve).	Reduction of endogenous stress: analgesia, sedation, anti-sympathetic therapy; Reduction of exogenous vasoconstriction: reduce the dose of norepinephrine to increase CO; methylene blue
	Cardiac Output (CO)	4. Is there any insufficiency/mismatch of	**Basis 1:** Gap > 6 **Basis 2:** Low ScvO2 without hypoxia, with "adequate"	No significant abnormality of ventricular function: fluid resuscitation, positive inotropes, heart rate

Key Element		Central Issues	Criterion	Therapeutic Options
		(CO)?	haemoglobin (assessed in conjunction with ScvO2) **Basis 3:** Presence of pre-obstruction (use of vasopressor drugs to passively maintain blood pressure)	regulation Significant impairment of right ventricular function: restoration of right ventricular function, e.g., lowering pulmonary arterial pressure (NO, prostaglandin, prone positioning, etc.) Complex cardiac conditions (e.g., valvular disease): modular assessment, valve flow analysis
	Systemic Congestion (C)	5. Is there any microcirculatory stasis? (caused by impaired venous return)	**Basis 1:** Delayed clearance on contrast-enhanced ultrasound **Basis 2:** Indirect evidence of impaired venous return, assessed via Vexus, showing a rounded inferior vena cava, hepatic vein siren sign, reduced or inverted S-wave, and interrupted renal venous flow spectrum, among other signs	Dehydration; Support for right heart function, etc.
Unregulated Host Response		6. What are the types of unregulated host response?	1. Immunoinflammatory dysregulation, based on: **Ultrasound findings of vascular paralysis:** blood flow and spectral analysis of the snuffbox **Ultrasound signs of endothelial damage:** symmetrical diffuse B-lines indicating pulmonary leakage **Elevated inflammatory markers:** IL-6, CRP, etc. 2. Neuroendocrine disorders, based on: Ultrasound evidence of respiratory hyperdrive, Ultrasound evidence of circulatory hyperdrive, Cardiac stress changes: apical asynchrony or incoordination, etc, Arterial and microcirculatory stress changes: snuffbox findings, contrast-enhanced imaging, etc.	**Neuroendocrine:** analgesia, sedation, anti-sympathetic therapy **Immuno-inflammatory:** endotoxin adsorption, cytokine adsorption, methylprednisolone, dexamethasone, loperhydrocodone, etc. **Coagulation:** anticoagulation **Metabolic bioenergetics:** cooling, analgesia, sedation, anti-sympathetic therapy

Key Element	Central Issues	Criterion	Therapeutic Options
		3. Metabolic bioenergetic disorders This version ensures a more precise alignment with medical terminology and improves readability.	
Lesion Search	7. What is the type of the primary cause?	Basis of infection, trauma, injury, pancreatitis, and others	**Drainage of lesions** (postural, puncture, surgical, etc.) **Haemostatic measures** (physical haemostasis, endoscopic, interventional, surgical, etc.)

Note: Lac, lactate; ScvO2, Central Venous Oxygen Saturation; GAP, venous-to-arterial CO_2 difference; CO, Cardiac Output; CPR, C-reactive protein;

The OPACCUS assessment system consists of the following seven areas:

1) **O (Oxygen Metabolism)**: Assesses inadequate oxygen supply, excessive oxygen consumption, oxygen utilization, and abnormal oxygen distribution.

2) **P (Microcirculatory Perfusion):** Evaluates peripheral microcirculatory perfusion index (PI), capillary refill time (CRT), and systemic mottling.

3) **A (Anterograde Arterial Vascular Tone and Resistance Assessment):** Assesses arterial conditions including high resistance, low resistance, high tone, and low tone states. This is primarily applied to the arterial blood flow spectrum and resistance index at the snuffbox artery.

4) **C (Stasis of Backward Venous Return):** Assesses venous congestion and grading using the ultrasound VeXUS protocol[63].

5) **C (Cardiac Output CO):** primarily determined by a combination of v-a CO2 GAP and ultrasound combined with traditional measures. The causes of CO insufficiency are further assessed and include left ventricular dynamic outflow tract obstruction, left heart under dynamics (coronary-related, stress-related, high volume, etc.), left heart end-diastolic volume preload insufficiency (diastolic dysfunction), right heart obstruction-pulmonary hypertension (pulmonary embolism, pulmonary origin e.g., ARDS, tension pneumothorax), right ventricular infarction-type right heart under dynamics, and total heart obstruction-pericardial origin (pericardial effusions, blood clots), venous return insufficiency (hypovolemia), intracardiac obstruction-new structural abnormalities of the heart (markedly abnormal intracardiac shunts, regurgitation, etc.).

6) **U (Systemic Organism Response):** Primarily assesses dysregulation in septic and non-septic inflammatory responses, coagulation, neuroendocrine responses, and metabolic bioenergetic abnormalities.

7) **S (Screening for Primary Disease):** Focuses on further identification and management of underlying conditions such as infections and hemorrhage.

2.6 Information Collection

The patient information collected includes:

- **Basic Information:** Age, gender, BMI, current medical history, past medical

history, and diagnosis.

- **Vital Signs:** Temperature (T), respiration rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and saturation of pulse oxygen (SpO2).
- **Bedside Arterial Blood Gas Analysis Results:** PaO2, PaCO2, oxygenation index (OI), blood lactate, and pH.
- **Laboratory Test Results:** Actual bicarbonate concentration, hemoglobin (Hb), interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT).
- **Critical Care Scores:** APACHE II score, SOFA score, Charlson Comorbidity Index (CCI), Richmond Agitation-Sedation Scale (RASS).
- **Traditional Hemodynamic Indicators:** Central venous pressure (CVP), capillary refill time (CRT), vasoactive-inotropic score (VIS), perfusion index, arterial-venous carbon dioxide gap (GAP), urine output, urine volume (prerenal or shock-related), 24-hour total fluid intake, and 24-hour total fluid output.
- **Treatment Details:** Use of ventilators, continuous renal replacement therapy (CRRT), and ultrasound.

VIS Score: The maximum dose of vasoactive drugs administered within the first 24 hours after shock diagnosis is recorded, and the VIS score is calculated according to the scoring principles established by Belletti [64].

Main Outcome

30-day Mortality Rate

Secondary Outcome Indicators:

- **Systemic Circulation Correction Time:** Calculated as the time from discharge minus the time of the maximum dose of vasoactive drugs administered during the enrollment period. If there are outliers, use Log10(time).
- **Microcirculatory Correction Time:** Calculated as the time from discharge minus the time of the highest lactate value recorded during the admission period. If there are abnormal values, use Log10(time).
- **Shock Improvement Time:** The time of the first observed "improvement." If no improvement is observed, the time is calculated as the "complete correction" time

minus the time of shock onset.

- **ICU Length of Stay (LOS):** The total number of days the patient spends in the ICU.
- **Total Hospital Length of Stay:** The total number of days the patient is hospitalized.
- **Duration of Ventilator Use:** The total number of days the patient requires mechanical ventilation.
- **ICU Costs:** The total costs incurred during the patient's ICU stay.
- **Total Hospitalization Costs:** The total costs incurred during the entire hospital stay.

2.7 Relevant Formulae

VIS Score: The maximum dose of vasoactive drugs administered during the first 24 hours after shock diagnosis is recorded, and the VIS score is calculated using the assignment principles set by Belletti A[64]. The specific formula for the VIS score is:

VIS=10,000×vasopressin dose (U/kg/min)+100×epinephrine dose (μg/kg/min)+100×norepinephrine dose (μg/kg/min)+50×levosimendan dose (μg/kg/min)+25×olprinone dose (μg/kg/min)+20×methylene blue dose (mg/kg/h)+10×milrinone dose (μg/kg/min)+10×phenylephrine dose (μg/kg/min)+10×terlipressin dose (μg/min)+0.25×angiotensin II dose (ng/kg/min)+dopamine dose (μg/kg/min)+dobutamine dose (μg/kg/min)+enoximone dose (μg/kg/min)

2.8 Research Groups

The OPACCUS execution rate was divided into three groups using the tertile method (all implementation rates were ranked from smallest to largest; the value at the 33.3% percentile was set at 0.5, and the value at the 66.7% percentile was set at 1):

- **Full Execution Group:** OPACCUS execution rate = 100%
- **Medium Execution Group:** 50% ≤ OPACCUS execution rate < 100%
- **Low Execution Group:** OPACCUS execution rate < 50%

These groups will be used to compare the impact of different levels of implementation on the prognosis of patients with shock.

3. Statistical analysis

This study employed a comprehensive statistical approach to analyze baseline characteristics and other clinical variables across different patient groups. For normally distributed measures, we used the mean ± standard deviation (Mean ± SD); for non-normally distributed measures, the median and interquartile range (IQR) were applied; and for count data, the frequencies were reported as n (%). The following statistical techniques were utilized:

- T-test: Employed to compare measures with a normal distribution.
- Chi-Square (χ^2) Test: Applied to compare categorical data.
- Wilcoxon Rank Sum Test: Used for comparing measures that are not normally distributed.

3.1 Impact of ICU Transfer Delays on the Prognosis of Shock Patients in General Wards

To assess the predictive value of pre-ICU shock time on in-hospital morbidity and mortality, we calculated the area under the receiver operating characteristic curve (AUC). Survival curves for 28 and 60 days were generated using the Kaplan-Meier method. Both univariate and multivariate logistic regression analyses were performed, with variables having a P-value < 0.05 in univariate analyses being included in the multivariate models to identify associations with mortality across the groups. Additionally, restricted cubic spline (RCS) modeling was employed to explore potential nonlinear relationships between pre-ICU shock time and in-hospital mortality. The efficacy of pre-ICU shock time as a predictive variable was further evaluated using ROC curves, with the AUC calculated to determine its predictive accuracy.

To evaluate the impact of early ultrasound use on in-hospital mortality in patients with shock, Kaplan-Meier survival curve analysis and logistic regression models were used to examine the association with in-hospital mortality and 28-day mortality.

A model for predicting in-hospital mortality in shock patients was also established by identifying influencing factors through univariate and multivariate logistic regression analysis. Model performance was evaluated using ROC curves, the Hosmer-Lemeshow test, calibration curves, and decision curve analysis.

3.2 Prognostic Impact of a New Visualized OPACCUS Diagnostic and Therapeutic Assessment Process for Shock Based on Etiology, hemodynamics, and Organism Response

For the prognostic analysis, a multivariable regression model was constructed, with the outcome at the time of discharge as the dependent variable, OPACCUS execute rate groups as the independent variable, and any imbalanced baseline factors between groups as covariates.

Handling of Missing Data:

Missing baseline indicators were filled using the Last Observation Carried Forward (LOCF) method, taking the first non-null observation within the initial 3 hours unless otherwise specified.

The dataset originally contained 87 variables. After excluding 29 variables with more than 40% missing data, 58 variables remained. Due to the complexity and ambiguity of the missing data patterns, the Random Forest method was employed to impute the missing values. All imputation processes were performed using the mice package in R, which requires minimal assumptions about the missing data patterns and provides effective imputation results.

After imputation, we compared the kernel density distribution of the data before and after imputation. The results indicated no statistically significant difference between the pre- and post-imputation data, suggesting that the imputed data is stable. A comparison of the data distributions before and after imputation is shown in Figure 1.

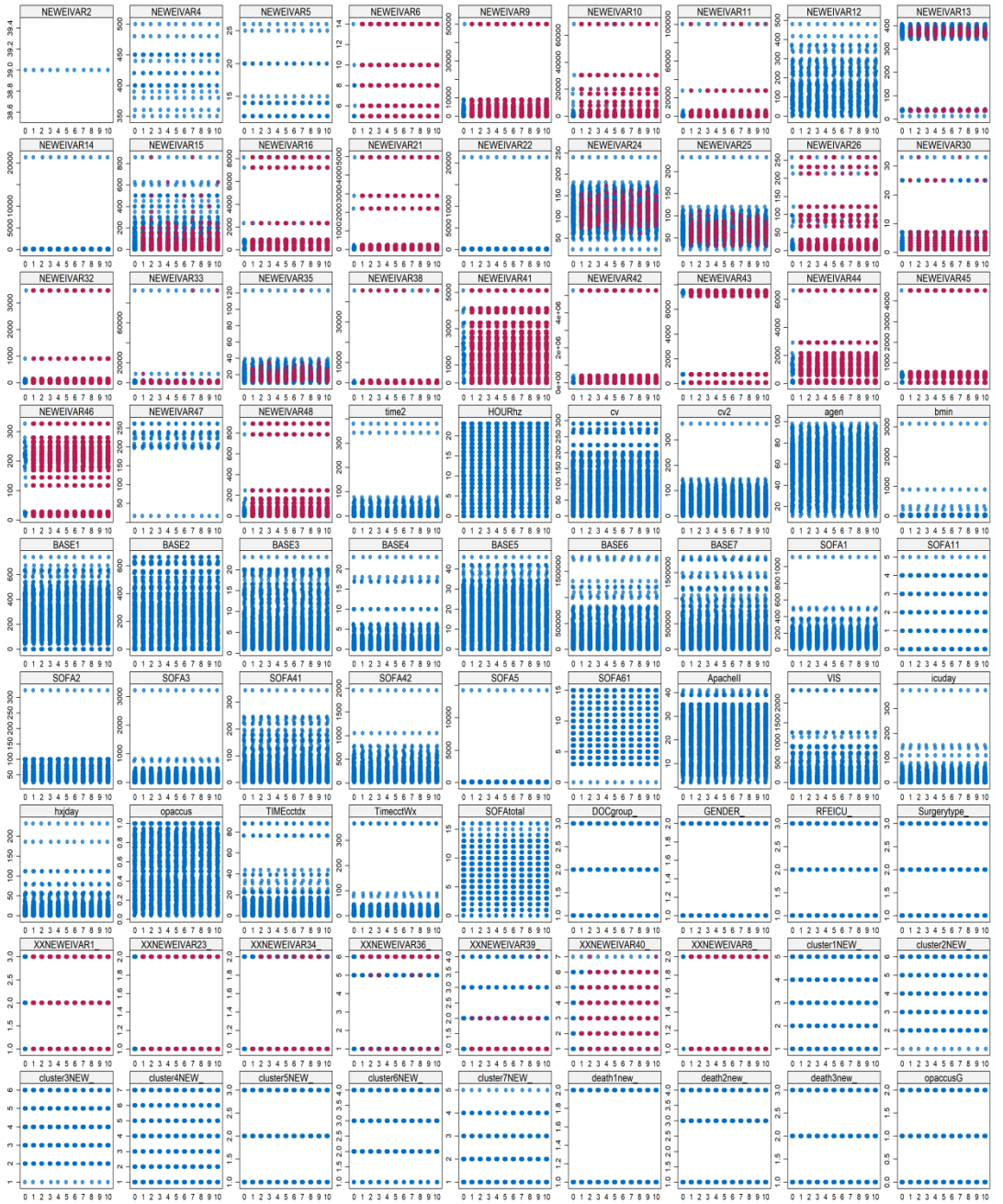


Figure 1: A comparison of the data distributions before and after imputation

Survival Analysis:

Due to the delayed effect (curve crossover) observed in the Kaplan-Meier (KM) curves for the OPACCUS execution rate subgroups and the failure to meet the proportional hazards assumption ($p < 0.05$), univariate analysis of OPACCUS was

performed using Landmark KM analysis. In the prognostic analysis, 17 patients had hospitalization durations ranging from 2 to 4 months, which significantly affected the model fit. These patients were excluded from the prognostic analysis, resulting in a total of 523 patients included in the analysis.

Multivariable analysis of survival data was conducted using restricted mean survival time (RMST). To account for the imbalance in censoring between groups at the cut-off point, the Inverse Probability of Censoring Weighting (IPCW) method was employed to weight the OPACCUS execution rate subgroups. IPCW regression assumes that the distribution of censoring can be correctly estimated, whereas pseudo-value regression does not require such an assumption.

The results of the KM analysis, shown in Figure 2-2, indicated a delayed effect in the KM curves across the three patient groups, with overlapping and crossing curves, leading to a reduced efficacy of the Log-rank test. The Supremum test demonstrated that the proportional hazards assumption was not satisfied for the OPACCUS execution rate subgroups, rendering the Log-rank test invalid. According to Fleming's test results in Table 2-5, there was no statistically significant difference between the three groups during the initial period of the 30-day timeframe ($P > 0.05$), while statistically significant differences were observed in the middle ($P = 0.0459$) and final segments ($P = 0.0399$).

To further clarify the differences between groups, Landmark analysis was conducted. The cut-off point was preliminarily determined to be around 6 days based on the KM curves. Landmark analysis results indicated no statistically significant difference between the three groups during the initial period (Log-rank $P = 0.1493$), whereas a statistically significant difference was observed during the later period (Log-rank $P = 0.0253$), as shown in Figure 2-3. However, the cut-off point for Landmark analysis was challenging to determine, and the cumulative martingale residual plots suggested that the proportional hazards assumption was not satisfied. Consequently, further univariate and multivariate analyses were performed using RMST. Supremum tests confirmed that the proportional hazards assumption was not met for the OPACCUS execution rate subgroups, making RMST the primary method for drawing

conclusions.

All statistical computations, analyses, and visualizations were conducted using PostgreSQL version 16.0 software, R programming version 4.4.0, and SAS 9.4 (version 9.4, SAS Institute, Inc., Cary, NC, USA). A P-value of < 0.05 was considered statistically significant.

Results

1. Evaluation of ICU Transfer Timing and Ultrasound-Guided Diagnosis and Treatment for the Prognosis of Shock Patients: Core Indicator Selection and Early Strategy Enhancement

1.1 Research Flowchart

Figure 1-1 illustrates the systematic process of participant selection and data collection for the study. It provides a visual representation of the steps involved, from initial screening to final inclusion in the study.

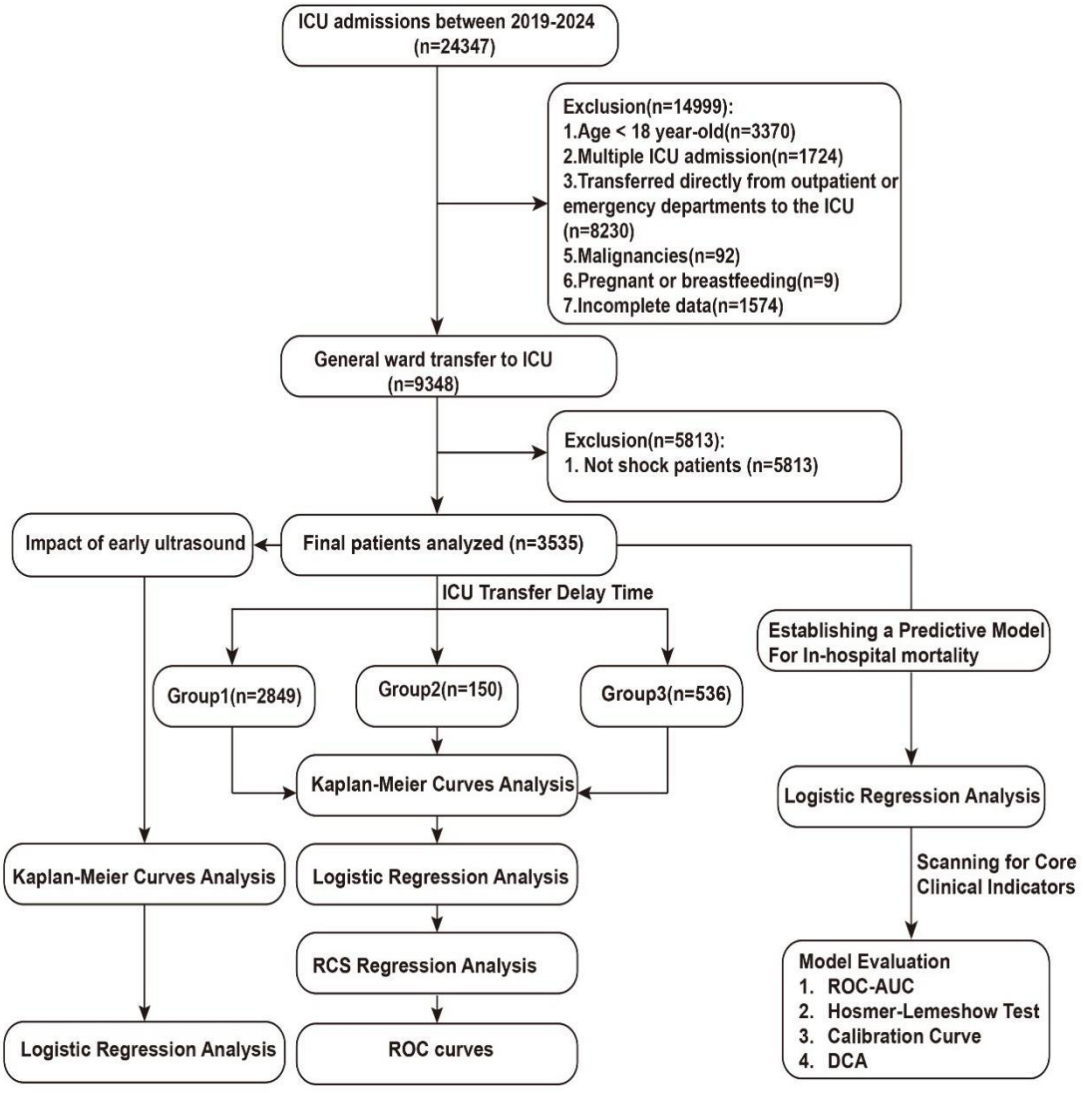


Figure 1-1: Flow chart of the Research Study population.

1.2 Description of Baseline Patient Information

1.2.1 Demography

Over a five-year period from January 1, 2019, to January 31, 2024, a total of 24,347 patients were admitted to the ICU at West China Hospital of Sichuan University. Out of these, 3,535 patients developed shock while in the general ward and were subsequently transferred to the ICU for specialized care. These patients met the inclusion criteria for the study and were included in the final analysis, representing a significant subset of ICU admissions associated with acute deterioration due to shock.

The demographic characteristics of the study population revealed a predominance of middle-aged to elderly patients, with an overall mean age of 56.4 ± 15.3 years. There was a marked male predominance in the cohort, with 2,317 male patients (65.5%) compared to 1,218 female patients (34.5%). The majority of patients were of Han Chinese ethnicity, comprising 1,981 individuals (56.0%), which reflects the general population distribution in the region served by the hospital.

The average length of hospitalization for these patients was 21.5 ± 21.7 days, with an average ICU stay of 7.77 ± 13 days. The total number of in-hospital deaths was 850, representing a mortality rate of 24.0%. The total duration time of shock was 39.6 ± 29.3 hours.

At the onset of shock, the median Sequential Organ Failure Assessment (SOFA) score was 11 (interquartile range: 9–12), and the median Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 26 (interquartile range: 22–29). Within the first 24 hours of ICU admission, the median SOFA score remained at 11 (interquartile range: 10–13), and the median APACHE II score was also 26 (interquartile range: 22–29). For a detailed overview of these baseline characteristics, refer to Table 1-1.

Table 1-1: General baseline of shock patients

Variables	All patients (n=3535)
Age, year	56.4 ± 15.3
Gender, n(%)	
Female	1218 (34.5%)
Male	2317 (65.5%)
Married, n(%)	
No	182 (5.15%)
Yes	3353 (94.9%)
Ethnicity, n(%)	
Han	1981 (56.0%)
Zangzu	126 (3.56%)
other	1428 (40.4%)
Severity score	
APACHE II (onset shock), IQR	26.0 [22.0; 29.0]
APACHE II (ICU first day), IQR	26.0 [22.0; 29.0]
SOFA (onset shock), IQR	11.0 [9.00;12.0]
SOFA (ICU first day), IQR	11.0 [10.0; 13.0]
Outcome	
Shock duration time, hour	39.6 ± 29.3
pre-ICU shock time, hour	5.29 ± 13.4
pos-ICU shock time, hour	34.3 ± 23.7
pre-shock time, hour	120 ± 284
Hospital stay time, day	21.5 ± 21.7
ICU stay time, day	7.77 ± 13.0
Hospital mortality, n(%)	
Alive	2685 (76.0%)
Death	850 (24.0%)
28-day mortality, n(%)	
Alive	2778 (78.6%)
Death	757 (21.4%)

Note: IQR, Interquartile Range (the median represents the continuity data); APACHE II score,

Acute Physiology, and Chronic Health Evaluation; SOFA score, Sequential Organ Failure Assessment; ICU, Intensive Care Unit; pre-ICU shock time, duration of transfer to the ICU after the onset of shock in the general ward; pos-ICU shock time, the period from the time the patient is admitted to the ICU while in a state of shock until the improvement of the shock condition; pre-shock time, the period from the time the patient is admitted to the ICU while in a state of shock until the improvement of the shock condition; pre-shock time, the duration from hospital admission to the onset of shock.

1.2.2 Clinical Characteristics of Shock Types

The study analyzed the distribution of different shock types among the 3,535 patients who were transferred to the ICU after developing shock in the general ward. The data revealed a clear predominance of distributive shock, which affected 2,392 patients, accounting for 67.7% of the cohort. This was followed by hypovolemic shock, observed in 1,099 patients (31.1%), cardiogenic shock in 123 patients (3.48%), and obstructive shock in 98 patients (2.77%). The prevalence of these shock types underscores the diverse etiological factors contributing to shock in critically ill patients and highlights the complex challenges faced by clinicians in managing these conditions. A closer examination of the subtypes of shock revealed that septic shock, a subtype of distributive shock, was the most common, accounting for 2,282 cases or 64.6% of all patients. Hemorrhagic shock, a subtype of hypovolemic shock, was the next most frequent, observed in 529 patients (15.0%).

Throughout the study period from 2019 to 2024, there was a discernible increase in the incidence of distributive shock, accompanied by a concerning trend of rising in-hospital mortality rates across all shock types. The mean duration of shock varied by type, with distributive shock lasting an average of 42.21 ± 29.89 hours, hypovolemic shock 36.55 ± 27.04 hours, cardiogenic shock 39.8 ± 33.32 hours, and obstructive shock 29.47 ± 26.94 hours. These clinical characteristics and trends are further detailed in Table 1-2 and illustrated in Figures 1-2 to 1-4.

Table 1-2: Types of shock clinical features

Variables	All patients (n=3535)
Septic shock, n(%)	
no	1253 (35.4%)
yes	2282 (64.6%)
Distributive shock, n(%)	
no	1143 (32.3%)
yes	2392 (67.7%)
Cardiac shock, n(%)	
no	3412 (96.5%)
yes	123 (3.48%)
Hypovolemic shock, n(%)	
no	2436 (68.9%)
yes	1099 (31.1%)
Obstructive shock, n(%)	
no	3437 (97.2%)
yes	98 (2.77%)
Hemorrhagic shock, n(%)	
no	3006 (85.0%)
yes	529 (15.0%)
Anaphylactic shock, n(%)	
no	3527 (99.8%)
yes	8 (0.23%)

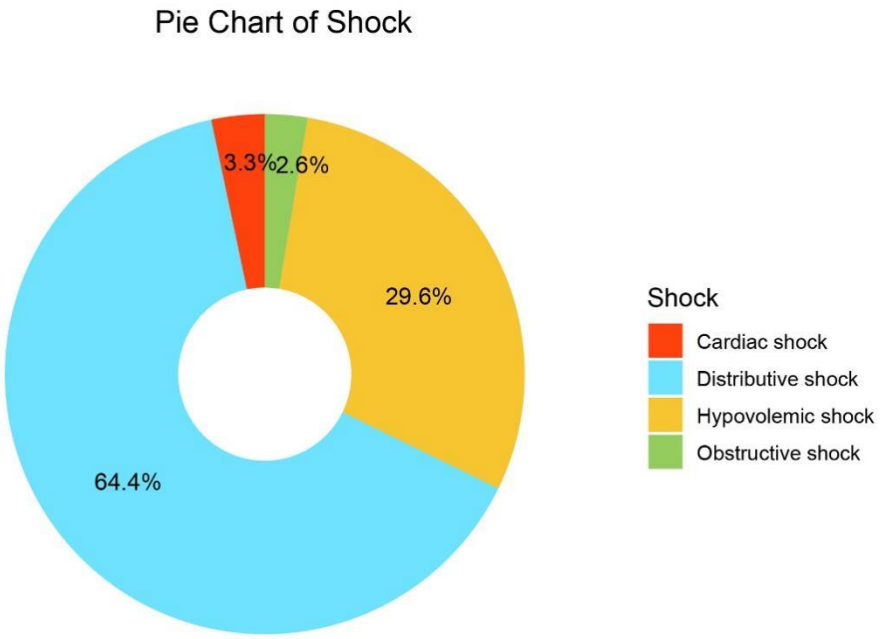
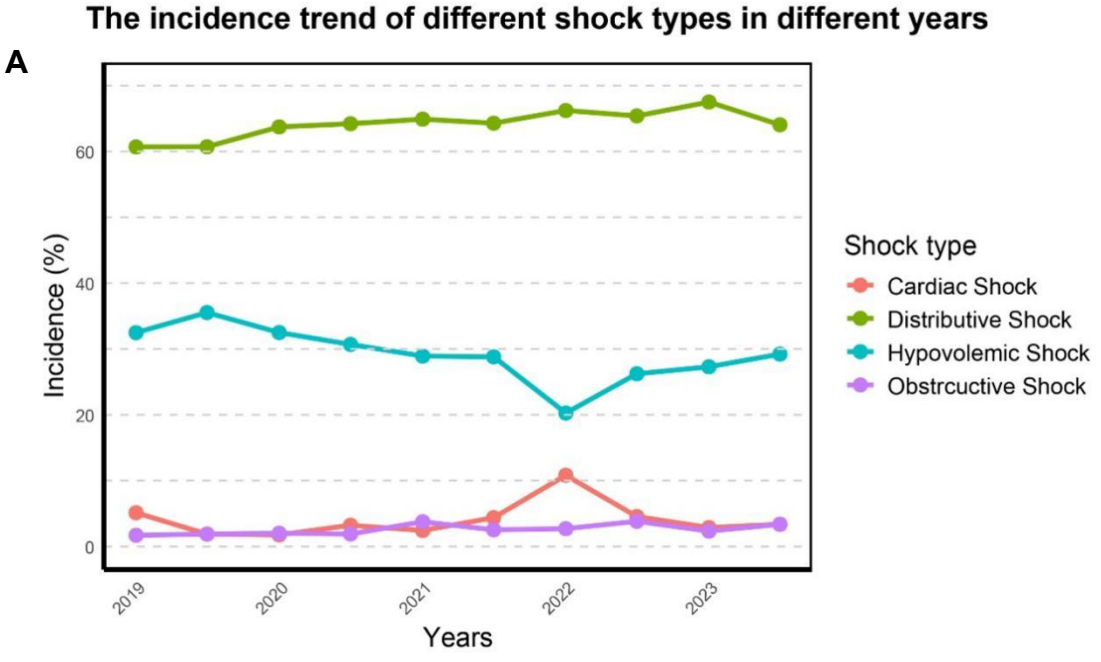


Figure 1-2: Proportions of Different Types of Shock



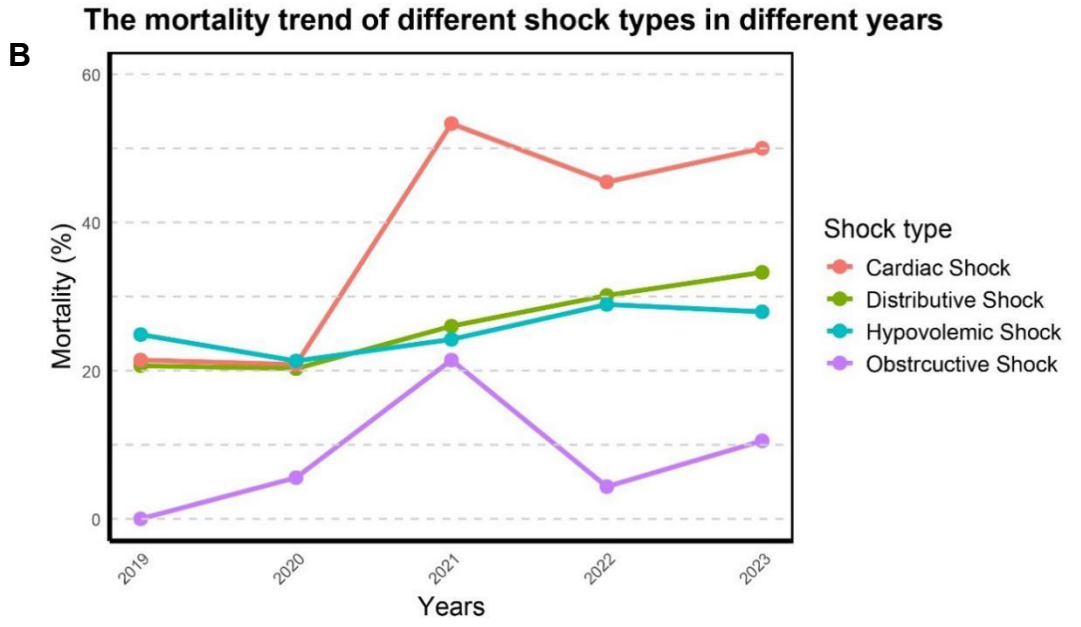


Figure 1-3: Incidence and Mortality Rates of Different Types of Shock by Year (2019 to 2024)

A: Incidence and Mortality of Different Types of Shock by Year

B: Mortality Rates of Different Types of Shock by Year

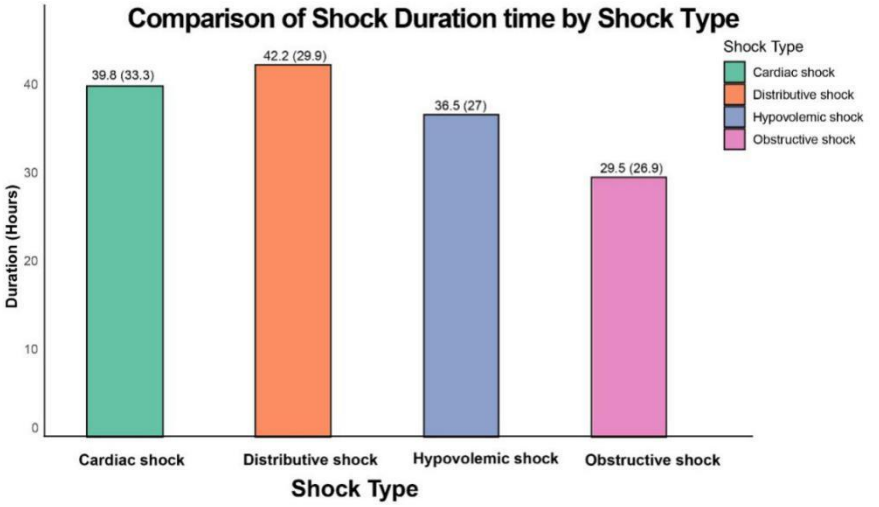


Figure 1-4: Comparison of Total Duration of Shock for Different Types (From Onset to Resolution)

Note: Over the past five years (2019 to 2024), the study found an increasing trend in the inpatient mortality rates for different types of shock. Among these, cardiogenic shock had the highest mortality rate, while obstructive shock had the lowest. these, cardiogenic shock had the highest mortality rate, while obstructive shock had the lowest.

1.2.3 Primary Diagnosis and Complications

The primary diagnoses among the study population are summarized in Table 1-3. Severe pneumonia emerged as the most prevalent diagnosis, affecting 1,882 patients (53.2%). Acute respiratory failure was identified in 650 patients (18.4%), while acute circulatory disorders were diagnosed in 375 patients (10.6%). Acute pancreatitis was present in 818 patients (23.1%), renal failure in 614 patients (17.4%), and liver failure in 996 patients (28.2%). Additionally, diseases of the central nervous system were diagnosed in 278 patients (7.86%), and diabetes was present in 586 patients (16.6%).

Complications were also notably significant within this cohort. A total of 89 patients (2.52%) experienced cardiac arrest and required cardiopulmonary resuscitation (CPR) during their admission.

Table 1-3: Primary diagnosis and complications

Variables	All patients (n=3535)
CPR :n(%)	
no	3446 (97.5%)
yes	89 (2.52%)
Respiratory failure: n(%)	
no	2885 (81.6%)
yes	650 (18.4%)
Pneumonia: n(%)	
no	1653 (46.8%)
yes	1882 (53.2%)
Circulatory disturbance: n(%)	
no	3160 (89.4%)
yes	375 (10.6%)
Acute pancreatitis: n(%)	
no	2717 (76.9%)
yes	818 (23.1%)
Central nervous system disease: n(%)	
no	3257 (92.1%)
yes	278 (7.86%)

Variables	All patients (n=3535)
Kidney failure: n(%)	
no	2921 (82.6%)
yes	614 (17.4%)
Diabetes: n(%)	
no	2949 (83.4%)
yes	586 (16.6%)
Liver failure: n(%)	
no	2539 (71.8%)
yes	996 (28.2%)

Note: CPR, Cardiopulmonary Resuscitation; MODS, Multiple Organ Dysfunction Syndrome.

1.3 Comparison of Baseline Characteristics for Subgroups of Delayed Transfers from the General Ward to the ICU for Patients Experiencing Shock

In this study, patients were stratified into three distinct groups based on the duration of time between the onset of shock and their subsequent transfer to the ICU. Group 1 consisted of patients transferred within less than 3 hours (n=2,849), Group 2 included those transferred within 3 to 6 hours (n=150), and Group 3 encompassed patients whose transfer occurred after more than 6 hours (n=536).

This grouping methodology was strategically chosen to reflect critical time windows for early intervention, with fluid resuscitation ideally initiated within 6 hours and specific shock management interventions optimally occurring within the first 3 hours. These time points are considered pivotal in influencing patient outcomes and were central to the analysis of delayed transfers in this study.

1.3.1 Main Diagnostic Features

In the first group, which consisted of patients transferred to the ICU within less than 3 hours after the onset of shock, the distribution of shock types and primary diagnoses reflected distinct clinical characteristics. Among these patients, 1,883 (66.1%) were diagnosed with distributive shock, 916 (32.2%) with hypovolemic shock, and 90 (3.16%) with cardiogenic shock, with the proportions of these shock types being lower compared to the other groups.

Regarding primary diagnoses, acute respiratory failure was present in 344 patients (12.1%), while severe pneumonia was the most prevalent condition, affecting 1,380 patients (48.4%). Circulatory disorders were diagnosed in 225 patients (7.90%), and acute pancreatitis was noted in 614 patients (21.6%). Additionally, central nervous system disorders were observed in 278 patients (7.86%), renal failure in 414 patients (14.5%), and liver failure in 725 patients (25.4%). Diabetes mellitus was diagnosed in 452 patients (15.9%), marking the lowest incidence of diabetes in the first group compared to the other groups.

Notably, only 39 patients (1.37%) in Group 1 required cardiopulmonary resuscitation (CPR), which was the lowest proportion across all groups, highlighting the potential benefits of earlier intervention in reducing the severity of clinical complications.

1.3.2 Various baseline vital signs and laboratory indicators

In this study, the baseline vital signs and laboratory indices of patients across the three groups were meticulously recorded and analyzed for statistical differences, as detailed in Table 1-4. The findings revealed significant variations among the groups, particularly in those patients who experienced prolonged delays before ICU transfer.

Within 24 hours of ICU admission, Group 3 (pre-ICU shock time >6 hours) exhibited notably higher severity scores and laboratory values. The median APACHE II score for this group was 28.0 [25.0; 31.0], while the median SOFA score reached 12.0 [11.0; 14.0]. These patients also had elevated respiratory rates at 22.8 ± 5.17 breaths per minute, a temperature of 37.8 ± 1.03°C, and a heart rate of 120 ± 27.6 beats per minute. Inflammatory and coagulation markers were similarly elevated, with C-reactive protein (CRP) levels at 127 ± 109 mg/L, an INR of 1.59 ± 0.84, and a troponin T (TnT) concentration of 181 ± 549 ng/mL. Additionally, metabolic indicators such as lactate (4.76 ± 4.71 mmol/L), sodium (145 ± 5.87 mmol/L), creatinine (149 ± 5.87 μmol/L), blood urea nitrogen (BUN) (11.9 ± 8.68 mg/dL), and blood glucose (10.8 ± 3.81 mmol/L) were significantly elevated in Group 3, reflecting the critical condition of these patients.

Conversely, within 24 hours post-ICU admission, Group 3 patients displayed

lower blood pressure readings, with diastolic blood pressure (DBP) at 52.5 ± 7.92 mmHg, systolic blood pressure (SBP) at 96.5 ± 15.4 mmHg, and mean blood pressure (MBP) at 67.9 ± 9.65 mmHg. Oxygenation indices such as SpO2 (97.8 ± 4.64%), PaO2 (94.2 ± 33.3 mmHg), and the PaO2/FiO2 ratio (223 ± 91 mmHg) were also lower compared to other groups. Hematological parameters, including erythrocyte count (3.47 ± 0.72 × 10^12/L), albumin (34.2 ± 6.44 g/L), hemoglobin (104 ± 20.5 g/L), and platelets (159 ± 105 × 10^9/L), were similarly compromised in this group.

These results underscore the significant physiological stress and deteriorating condition associated with delayed ICU transfer, particularly beyond the 6-hour mark.

Table 1-4: Comparison of Baseline Characteristics for Patient Groups Based on Pre-ICU Shock Time (Duration from Onset of Shock in General Ward to Transfer The following is a summary of the baseline characteristics for patient groups based on)

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P-value
Gender, Male n (%)	1861 (65.3%)	98 (65.3%)	358 (66.8%)	0.805
Age(year)	56.2 ± 15.4	58.1 ± 15.2	57.1 ± 14.9	0.181
Married, n (%)	2709 (95.1%)	144 (96.0%)	500 (93.3%)	0.180
Ethnicity, n(%)				<0.001
Han	1654 (58.1%)	83 (55.3%)	244 (45.5%)	
Zangzu	104 (3.65%)	6 (4.00%)	16 (2.99%)	
other	1091 (38.3%)	61 (40.7%)	276 (51.5%)	
Severity score				
Apache II (onset shock)	25.0 [22.0; 28.0]	27.0 [23.0; 30.0]	31.0 [28.0; 33.0]	<0.001
Apache II (ICU first day)	25.0 [22.0; 28.0]	27.0 [23.2; 31.0]	28.0 [25.0; 31.0]	<0.001
SOFA (onset shock)	11.0 [10.0; 12.0]	11.0 [9.00;12.0]	9.00 [7.00;11.0]	<0.001
SOFA (ICU first day)	11.0 [10.0; 12.0]	12.0 [11.0; 13.0]	12.0 [11.0; 14.0]	<0.001
Type shock				
Septic shock, n (%)	1783 (62.6%)	95 (63.3%)	404 (75.4%)	<0.001
Cardiac shock, n (%)	90 (3.16%)	10 (6.67%)	23 (4.29%)	0.040
Hypovolemic shock, n (%)	916 (32.2%)	51 (34.0%)	132 (24.6%)	0.002
Hemorrhagic shock, n(%)	406 (14.3%)	36 (24.0%)	87 (16.2%)	0.003
Obstructive shock, n (%)	87 (3.05%)	4 (2.67%)	7 (1.31%)	0.068
Anaphylactic shock, n (%)	7 (0.25%)	1 (0.67%)	0 (0.00%)	0.279
Distributive shock, n (%)	1883 (66.1%)	98 (65.3%)	411 (76.7%)	<0.001
Comorbidity				

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P-value
CPR, n (%)	39 (1.37%)	11 (7.33%)	39 (7.28%)	<0.001
Respiratory failure, n (%)	344 (12.1%)	55 (36.7%)	251 (46.8%)	<0.001
Pneumonia, n (%)	1380 (48.4%)	89 (59.3%)	413 (77.1%)	<0.001
Circulatory disturbance, n (%)	225 (7.90%)	29 (19.3%)	121 (22.6%)	<0.001
Acute pancreatitis, n (%)	614 (21.6%)	34 (22.7%)	170 (31.7%)	<0.001
Central nervous system disease, n (%)	207 (7.27%)	12 (8.00%)	59 (11.0%)	0.013
Kidney failure, n (%)	414 (14.5%)	38 (25.3%)	162 (30.2%)	<0.001
Diabetes, n (%)	452 (15.9%)	27 (18.0%)	107 (20.0%)	0.058
Liver failure, n(%)	725 (25.4%)	47 (31.3%)	224 (41.8%)	<0.001
Vital signs				
DBP, (mmHg)	52.5 ± 7.92	51.0 ± 9.33	50.6 ± 9.65	<0.001
SBP, (mmHg)	96.5 ± 15.4	90.9 ± 15.3	92.1 ± 17.1	<0.001
MAP, (mmHg)	67.9 ± 9.65	64.9 ± 11.1	65.0 ± 10.9	<0.001
Respiratory rate ,(min^{-1})	21.5 ± 4.14	22.5 ± 5.30	22.8 ± 5.17	<0.001
Temperature, (C)	37.4 ± 0.80	37.4 ± 0.92	37.8 ± 1.03	<0.001
Heart rate, (bmp)	109 ± 20.5	115 ± 21.7	120 ± 27.6	<0.001
Laboratory Test				
AST/ALT ratio	1.92 ± 1.16	2.08 ± 1.06	2.07 ± 1.88	0.017
C-reaction protein, (mg/L)	78.8 ± 82.8	101 ± 87.1	127 ± 109	<0.001
eGFR,(ml/min)	90.6 ± 29.5	75.7 ± 32.3	74.6 ± 7	<0.001
INR	1.49 ± 0.62	1.56 ± 0.53	1.59 ± 0.84	0.003
MB, (U/L)	8.15 ± 22.8	15.8 ± 42.1	12.3 ± 33.2	<0.001
PaCO2, (mmHg)	42.5 ± 6.81	46.4 ± 13.7	45.3 ± 11.1	<0.001
SPO2, (%)	97.8 ± 4.64	95.9 ± 7.27	96.5 ± 5.07	<0.001
PaO2, (mmHg)	94.2 ± 33.3	83.7 ± 34	78.7 ± 36.1	<0.001
FiO2, (%)	44.3 ± 9.69	53.1 ± 16.1	54.4 ± 15.5	<0.001
PaO2/FiO2 ratio, (mmHg)	223 ± 91.0	174 ± 87.4	160 ± 90.4	<0.001
RBC,(g/L)	3.47 ± 0.72	3.45 ± 0.73	3.24 ± 0.79	<0.001
Albumin	34.2 ± 6.44	33.3 ± 5.94	33.6 ± 5.70	0.075
WBC, ($\times 10^9$ /L)	13.6 ± 6.86	14.1 ± 8.66	13.9 ± 8.67	0.469
Monocyte absolute	0.76 ± 0.50	0.72 ± 0.51	0.72 ± 0.48	0.162
TnT, (ng/L)	77.5 ± 293	165 ± 426	181 ± 549	<0.001
Potassium, (mmol/L)	3.47 ± 0.72	3.45 ± 0.73	3.24 ± 0.79	<0.001
Lactate, (mmol/L)	3.83 ± 3.19	4.73 ± 4.69	4.76 ± 4.71	<0.001
Lymphocyte, ($\times 10^9$ /L)	1.11 ± 0.85	0.97 ± 0.93	0.96 ± 0.74	<0.001
Sodium, (mmol/L)	143 ± 5.32	144 ± 4.77	145 ± 5.87	<0.001
Creatinine, (μmol/L)	103 ± 92.3	130 ± 103	149 ± 134	<0.001

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P-value
Bun, (mmol/L)	8.03 ± 5.75	10.1 ± 6.77	11.9 ± 8.68	<0.001
PPT, (s)	20.0 ± 9.31	21.8 ± 12.1	19.2 ± 7.24	0.007
Glucose, (mmol/L)	10.7 ± 3.73	10.6 ± 3.38	10.8 ± 3.81	0.808
Hemoglobin, (g/L)	104 ± 20.5	101 ± 22.3	97.8 ± 23.2	<0.001
Platelet, ($\times 10^9$ /L)	159 ± 105	142 ± 91.3	128 ± 82.2	<0.001
Anion gap, (mmol/L)	19.6 ± 5.25	20.4 ± 6.17	20.2 ± 6.33	0.040

Note: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; DBP, Diastolic Blood Pressure; SBP. Diastolic Blood Pressure; SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; eGFR, estimated Glomerular Filtration Rate; MB, serum myoglobin; INR, International Normalized Ratio; TnT, Troponin T; PPT, Partial Prothrombin Time; AG, Anion Gap; MODS. Multiple Organ Dysfunction Syndrome; CPR, Cardiopulmonary Resuscitation; RBC, Red Blood Cells; WBC, white blood cells.

1.3.3 Comparative Characteristics of Laboratory Indicators Over the First Three Days after admission to the ICU

The analysis of blood lactate levels over the first 72 hours following ICU admission revealed a significant downward trend across all three groups, with distinct differences between them.

For Group 1 (pre-ICU shock time <3 hours), the blood lactate levels were observed to be 3.63 ± 3.12 mmol/L at the 6th hour, 2.78 ± 2.44 mmol/L at the 24th hour, 2.05 ± 1.67 mmol/L at the 48th hour, and 1.93 ± 1.62 mmol/L at the 72nd hour. This group consistently exhibited the lowest lactate levels, indicative of more effective early intervention.

In contrast, Group 2 (pre-ICU shock time: 3-6 hours) showed higher initial lactate levels, starting at 4.75 ± 4.58 mmol/L at the 6th hour, then decreasing to 3.18 ± 3.62 mmol/L at the 24th hour, 2.38 ± 2.11 mmol/L at the 48th hour, and reaching 2.01 ± 1.23 mmol/L by the 72nd hour.

Group 3 (pre-ICU shock time >6 hours) presented the highest lactate levels, starting at 4.72 ± 4.29 mmol/L at the 6th hour, decreasing to 3.31 ± 3.29 mmol/L at the 24th hour, 2.83 ± 2.75 mmol/L at the 48th hour, and finally reaching 2.42 ± 1.98

mmol/L at the 72nd hour. Despite the overall decline, this group's lactate levels remained consistently higher than those in Groups 1 and 2, reflecting the delayed intervention and more severe metabolic derangement.

This pattern of decreasing blood lactate levels, though consistent across all groups, was notably more pronounced and achieved more rapidly in Group 1, underscoring the importance of timely ICU transfer in the management of shock. Detailed findings are provided in Table 5 and illustrated in Figure 1-5.

Similarly, analyses of other critical laboratory indicators such as blood creatinine, platelet count, and troponin T (TnT) levels also demonstrated a gradual reduction at 24, 48, and 72 hours post-ICU admission across all groups. Group 1 again exhibited the lowest levels, reinforcing the impact of early intervention. The results are further elaborated in Table 1-5 and depicted in Figures 1-6 to 1-8.

Table 1-5: Comparison of Laboratory Indicators Over the First Three Days After ICU Admission by Patient Groups Based on Pre-ICU Shock Time.

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P value
lactate 6h	3.63±3.12	4.75±4.58	4.72±4.29	<0.001
lactate 24h	2.78±2.44	3.18±3.62	3.31±3.29	<0.001
lactate 48h	2.05±1.67	2.38±2.11	2.83±2.75	<0.001
lactate 72h	1.93±1.62	2.01±1.23	2.42±1.98	<0.001
platelet 24h	140±98.4	121±85.0	109±76.6	<0.001
platelet 48h	120±88.5	110±73.3	101±74.9	0.001
platelet 72h	120±89.5	115±70.5	108±74.9	0.055
Cr 24h	95.2±86.6	125±103	146±136	<0.001
Cr 48h	96.0±72.7	110±79.8	119±87.5	<0.001
Cr 72h	90.5±74.3	102±80.4	102±68.7	0.022
TnT 24h	65.5±299	150±381	172±516	<0.001
TnT 48h	82.5±279	179±547	197±590	<0.001
TnT 72h	84.2±268	133±431	182±684	0.016

Note: Cr, Serum Creatinine; TnT, Troponin T.

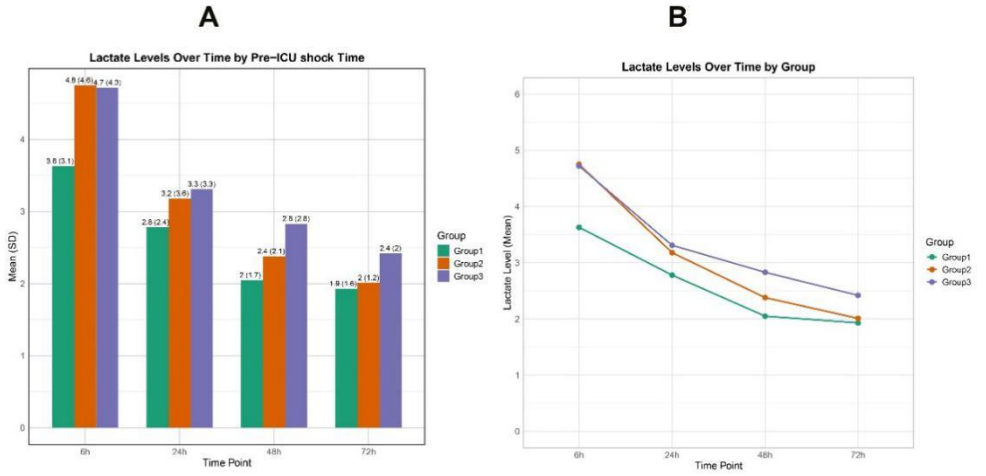


Figure 1-5: Lactate Levels Over Time (Comparison of the First Three Days After ICU Admission) by Pre-ICU Shock Time Groups.

Note: A: Bar chart comparing blood lactate levels at various time points after ICU admission among different pre-ICU shock time groups. **B:** Line plot with markers comparing blood lactate levels at different time points after ICU admission among pre-ICU shock time groups.

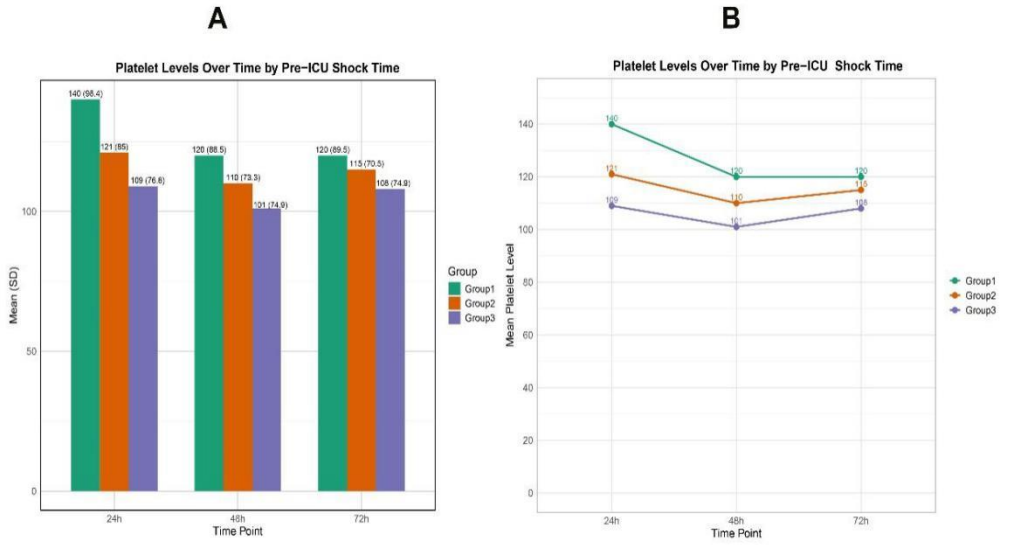


Figure 1-6: Platelet Levels Over Time (Comparison of the First Three Days After ICU Admission) by Pre-ICU Shock Time Groups.

Note: Bar chart comparing platelet levels at various time points after ICU admission among different pre-ICU shock time groups. **B:** Line plot with markers comparing platelet levels at different time points after ICU admission among pre-ICU shock time groups.

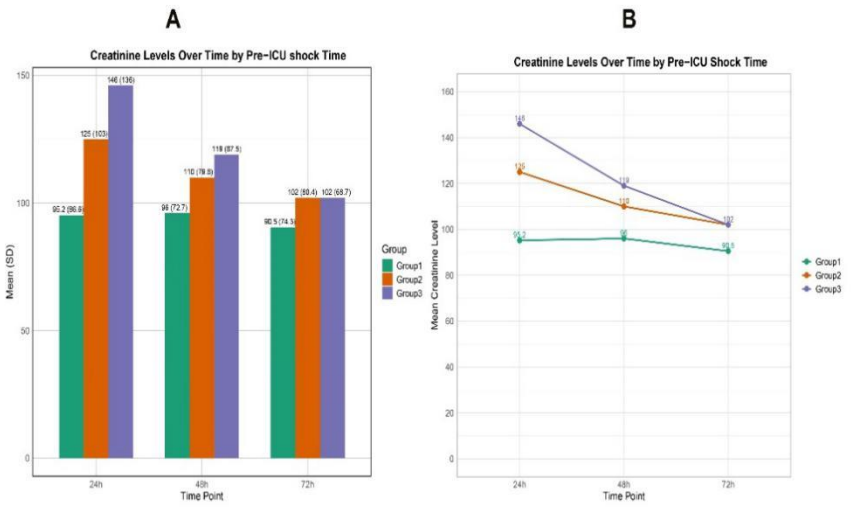


Figure 1-7: Creatinine Levels Over Time (Comparison of the First Three Days After ICU Admission) by Pre-ICU Shock Time Groups.

Note: Bar chart comparing creatinine levels at various time points after ICU admission among different pre-ICU shock time groups. **B:** Line plot with markers comparing creatinine levels at different time points after ICU admission among pre-ICU shock time groups. markers comparing creatinine levels at different time points after ICU admission among pre-ICU shock time groups.

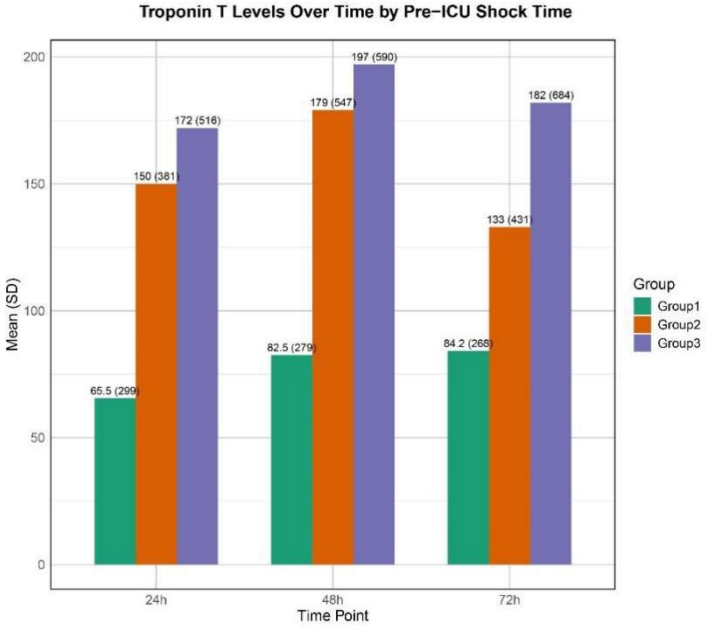


Figure 1-8: Troponine T Levels Over Time (Comparison of the First Three Days After ICU Admission) by Pre-ICU Shock Time Groups.

1.3.4 Treatment and Handling

1.3.4.1 Comparison of Duration of Mechanical Ventilation

In this study, the duration of mechanical ventilation was compared across the three groups of patients, revealing significant differences (P<0.001). The first group (pre-ICU shock time <3 hours) had the shortest duration of mechanical ventilation, averaging 98.0 ± 165 hours. In contrast, the second group (pre-ICU shock time: 3-6 hours) required a significantly longer duration, with an average of 214 ± 440 hours. The third group (pre-ICU shock time >6 hours) experienced the longest duration of mechanical ventilation, averaging 240 ± 280 hours.

These findings highlight the impact of delayed ICU transfer on the necessity for prolonged mechanical ventilation, with patients experiencing earlier ICU intervention requiring significantly shorter mechanical support. The extended duration in Groups 2 and 3 suggests more severe respiratory compromise and a greater need for mechanical assistance, likely due to delayed resuscitative efforts and the progression of shock before ICU admission. Detailed data are presented in Table 1-6.

Table 1-6: Comparison of Mechanical Ventilation Duration Among Patient Groups Based on Pre-ICU Shock Time

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P-value
Total ventilator time (hours)	98.0 ± 165	214 ± 440	240 ± 280	0.001

1.3.4.2 Comparison of the use of ultrasound

This study evaluated the utilization of ultrasonography within two critical time frames: within 6 hours after the onset of shock and within 24 hours of ICU admission.

Ultrasonography Use Within 6 Hours After Shock Onset:

The analysis revealed that ultrasonography was employed in 192 patients (6.74%) in the first group (pre-ICU shock time <3 hours), 6 patients (4.00%) in the second group (pre-ICU shock time: 3-6 hours), and 12 patients (2.24%) in the third group (pre-ICU shock time >6 hours). The first group had the highest likelihood of undergoing ultrasonography within this early intervention window, with a statistically significant difference observed among the groups (P<0.001). These results suggest that earlier

ICU admission correlates with a higher probability of ultrasonography use shortly after shock onset, potentially reflecting a more proactive approach to diagnosis and management in the early phases of shock. Detailed data are provided in Table 1-7.

Ultrasonography Use Within 24 Hours of ICU Admission:

When considering the use of ultrasonography within the first 24 hours of ICU admission, the rates were 1,182 patients (41.5%) in the first group, 64 patients (42.7%) in the second group, and 225 patients (42.0%) in the third group. Interestingly, there was no statistically significant difference in ultrasonography use among the three groups during this period (P=0.94). This indicates that, regardless of the timing of ICU admission, ultrasonography was commonly utilized across all groups within the first 24 hours, suggesting it is a standard diagnostic tool once patients are stabilized in the ICU.

Table 1-7: Comparison of Ultrasound Use Proportions Among Patient Groups Based on Pre-ICU Shock Time

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P-value
Ultrasound Within 6h of Shock	192 (6.74%)	6 (4.00%)	12 (2.24%)	<0.001
ICU Ultrasound Within 24h	1182 (41.5%)	64 (42.7%)	225 (42.0%)	0.944

1.3.4.3 Comparison of Norepinephrine Use

This study analyzed the total amount of norepinephrine administered across the three groups, revealing significant differences:

Total Norepinephrine Use: The average total norepinephrine usage was 32.1 ± 70.0 mg in Group 1 (pre-ICU shock time <3 hours), 69.1 ± 89.8 mg in Group 2 (pre-ICU shock time: 3-6 hours), and 104 ± 154 mg in Group 3 (pre-ICU shock time >6 hours). Group 3 had the highest total amount of norepinephrine administered, reflecting more severe shock and a greater need for vasopressor support due to delayed intervention. This difference was statistically significant (P<0.001).

Norepinephrine Use During ICU Admission: The analysis of norepinephrine use during ICU admission showed values of 31.8 ± 69.8 mg in Group 1, 66.1 ± 79.5 mg in Group 2, and 97.4 ± 144 mg in Group 3. The highest norepinephrine usage was observed in Group 3, corresponding to the prolonged pre-ICU shock time and the

subsequent escalation of shock severity. Conversely, Group 1 had the lowest norepinephrine usage, consistent with the earlier intervention and potentially less severe shock condition upon ICU admission. This difference was also statistically significant (P<0.001). See Table 1-8.

Table 1-8: Comparison of Norepinephrine Usage Among Patient Groups Based on Pre-ICU Shock Time

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P-value
Total Norepinephrine Usage, mg	32.1 ± 70.0	69.1 ± 89.8	104 ± 154	0.001
Total Norepinephrine for Pre-ICU Shock Time, mg	0.00 ± 0.07	0.00 ± 0.00	0.00 ± 0.00	0.887
Total Norepinephrine in ICU, mg	31.8 ± 69.8	66.1 ± 79.5	97.4 ± 144	0.001

1.3.4.4 Comparison of Early Antibiotic Use

This study examined the administration of antibiotics within critical time windows around the onset of shock and ICU admission, revealing notable differences among the groups:

Antibiotic Use Within 6 Hours After Shock Onset: Among patients who experienced shock, 901 (31.6%) in Group 1 (pre-ICU shock time <3 hours) received antibiotics within 6 hours after shock onset, compared to 34 (22.7%) in Group 2 (pre-ICU shock time: 3-6 hours) and 54 (10.1%) in Group 3 (pre-ICU shock time >6 hours). Group 1 had the highest rate of early antibiotic administration, significantly higher than the other groups (P<0.001). This suggests a more proactive approach to initiating antibiotic therapy in patients who were transferred to the ICU earlier, potentially reflecting the critical role of early intervention in managing infections associated with shock.

Antibiotic Use Within 6 Hours of ICU Admission: Within the first 6 hours of ICU admission, 898 (31.5%) of patients in Group 1 received antibiotics, 46 (30.7%) in Group 2, and 101 (18.8%) in Group 3. Again, Group 1 demonstrated the highest use of antibiotics, with a significant difference compared to the other groups (P<0.001). This continued trend underscores the importance of early antibiotic therapy in patients who were transferred to the ICU promptly, highlighting its critical role in improving

outcomes by addressing infections rapidly.

These findings emphasize the importance of early antibiotic administration in the management of shock, particularly in patients with prompt ICU transfer, where timely treatment may impact overall clinical outcomes. Detailed results are shown in Table 1-9.

Table 1-9: Comparison of Antibiotic Usage Among Patient Groups Based on Pre-ICU Shock Time

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P-value
Antibiotic usage within 6h of shock	901 (31.6%)	34 (22.7%)	54 (10.1%)	<0.001
ICU Antibiotic usage within 6h	898 (31.5%)	46 (30.7%)	101 (18.8%)	<0.001

1.3.5 Comparison of transferred working days

This study assessed the timing of shock onset and ICU transfer in relation to working hours and non-working hours, revealing the following insights:

Occurrence of Shock During Working vs. Non-Working Hours: Analysis showed that 1253 (44.0%) patients in Group 1 (pre-ICU shock time <3 hours) experienced shock during non-working hours. In Group 2 (pre-ICU shock time: 3-6 hours), 38 (25.3%) patients had shock during non-working hours, while in Group 3 (pre-ICU shock time >6 hours), 252 (47.0%) patients experienced shock during non-working hours. Group 3 had the highest percentage of patients with shock occurring during non-working hours, indicating a potential delay in recognition or management of shock outside regular working hours. Despite these observations, statistical analysis revealed no significant difference between the groups regarding the occurrence of shock during weekdays (Monday to Friday) versus weekends (Saturday/Sunday) (P=0.075).

Timing of ICU Transfer Relative to Working Hours: When examining the timing of ICU transfers from general wards, no statistically significant difference was found between the three groups in terms of transfer occurring on weekdays versus weekends (P=0.112). However, a higher percentage of transfers during non-working hours was observed in Group 1 (46.2%) compared to Group 2 (34.0%) and Group 3

(37.1%). This suggests a trend where earlier ICU transfers (Group 1) might be more frequently occurring during non-working hours compared to later transfers.

These findings highlight the influence of non-working hours on both the onset of shock and the timing of ICU transfers, although the statistical significance was not evident for the timing of transfers. Detailed results are presented in Table 1-10.

Table 1-10: Comparison of Working Time by Pre-ICU Shock Time Groups

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P-value
shock onset, n(%)				<0.001
On-Hours	1596 (56.0%)	112 (74.7%)	284 (53.0%)	
Off-Hours	1253 (44.0%)	38 (25.3%)	252 (47.0%)	
shock day, n(%)				0.075
Monday to Friday	2200 (77.2%)	125 (83.3%)	400 (74.6%)	
Saturday/Sunday	649 (22.8%)	25 (16.7%)	136 (25.4%)	
ICU Departure day, n(%)				0.112
Monday to Friday	2194 (77.0%)	124 (82.7%)	400 (74.6%)	
Saturday/Sunday	655 (23.0%)	26 (17.3%)	136 (25.4%)	
ICU Departure Time, n(%)				<0.001
On-Hours	1534 (53.8%)	99 (66.0%)	337 (62.9%)	
Off-Hours	1315 (46.2%)	51 (34.0%)	199 (37.1%)	
ICU Departure work day, n(%)				<0.001
Work hours	1080 (37.9%)	52 (34.7%)	286 (53.4%)	
Work-off hours	1769 (62.1%)	98 (65.3%)	250 (46.6%)	

Note: On-Hours: Monday to Friday from 7:00 a.m. to 10:59 p.m; Off-Hours: Monday to Friday from 11:00 p.m. to 6:59 a.m., and all day Saturday and Sunday; Work hours, every day from 8:00 am to 5:59 p.m; Work-off hours, every day from 6:00 p.m to 7:59 am. Hours: Monday to Friday from 11:00 p.m. to 6:59 a.m., and all day Saturday and Sunday; Work hours, every day from 8:00 am to 5:59 p.m; Work-off hours, every day from 6:00 p.m to 7:59 am.

1.3.6 Comparison of total time characteristics of occurrence of shock

When comparing the total shock duration time of the three groups of patients, it was found that the total shock duration time of the first group was the shortest, with an average of 32.8±23.4 hours; while the total shock duration time of the third group

was the longest, with an average of 75.6±32.4 hours, and the difference was statistically significant (P<0.001). Further analysis of the shock duration time after admission to the ICU showed that patients in the first group also had the shortest shock time in the ICU, with an average of 32.3±23.4 hours; while patients in the third group had the longest shock duration time, with an average of 44.9±22.8 hours, again with a significant difference (P<0.001). See Table 1-11.

Table 1-11: Comparison of Shock Duration Time by Pre-ICU Shock Time Groups

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P value
Shock duration time, hours	32.8 ± 23.4	39.2 ± 24.2	75.6 ± 32.4	<0.001

1.3.7 Comparison of days in hospital and days in ICU

Comparing the total hospitalization days of patients in the three groups, patients in the first group had the shortest hospitalization days, with an average of 19.9±17.9 days; patients in the third group had the longest hospitalization days, with an average of 29.1±32.5 days, with a significant difference (P<0.001). In terms of ICU hospitalization days, patients in the first group had the shortest ICU hospitalization days, with an average of 6.83±10.2 days; patients in the third group had the longest ICU hospitalization days, with an average of 12.5±22.3 days, and the difference was equally significant (P<0.001). See Table 1-12.

Table 1-12: Comparison of Hospital and ICU Stay Times by Pre-ICU Shock Time Groups

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P value
Hospital stay time, days	19.9 ± 17.9	24.5 ± 31.2	29.1 ± 32.5	<0.001
ICU stay time, days	6.83 ± 10.2	8.88 ± 11.0	12.5 ± 22.3	<0.001

1.3.8 Comparison of mortality rates among the three groups

Analyzing the in-hospital mortality rates of the three groups of patients, the first group had the lowest mortality rate with 513 patients (18.0%), the second group had a higher mortality rate with 61 patients (40.7%), and the third group had the highest mortality rate with 276 patients (51.5%). The hospitalized mortality rate was significantly lower in the first group than in the other two groups, while the mortality rate in the third group was significantly higher than in the other two groups. See Table

1-13.

Table 1-13: Comparison of Hospital and ICU 28-day mortality by Pre-ICU Shock Time Groups

Variables	Group1 N=2849	Group2 N=150	Group3 N=536	P value
Hospital mortality, n (%)	513 (18.0%)	61 (40.7%)	276 (51.5%)	<0.001
ICU 28-day mortality, n (%)	458 (16.1%)	57 (38.0%)	242 (45.1%)	<0.001

1.4 Comparative characteristics of the basic data of patients in the hospitalized survival group and the death group

A total of 3535 patients were enrolled with a total of 2685 (76.0%) in the survival group and 850 (24.0%) in the hospitalized deaths. The age, Ethnicity, APACHE II score, SOFA score, working holiday for shock, total shock time, pre-ICU shock time group, pre-ICU shock time, Pos-ICU shock time, hospital stay time, ICU stay time, Cardiac shock, Obstructive shock, Distributive shock, septic shock, hemorrhagic shock, MODS, CPR, Respiratory failure, pneumonia, circulatory disturbance, acute pancreatitis, central nervous system disease, Kidney failure, Diabetes, liver failure, DBP, SBP, MAP, Respiratory DBP, SBP, MAP, Respiratory rate, Temperature, heart rate, AST/ALT ratio, C reaction protein, INR, eGFR, MB, PaCO2, RBC, albumin, WBC, monocyte absolute, TnT, K, Lactate lymphocyte, Na, BUN, PPT, glucose, Hemoglobin, platelet, SpO2, PaO2, Cr, AG, Platelet, Hemoglobin, antibiotic Shock 6h, antibiotic ICU 6h, Total ventilator time, total NE, Ultrasound shock 6h, ultrasound ICU 6h, the difference was statistically significant ($p<0.05$). While the differences in gender, marriage, SOFA (onset shock), Hypovolemic shock, anaphylactic shock, ultrasound 12h, and ultrasound ICU 24h were not statistically significant ($P>0.05$). See Table 14.

Table 1-14: Comparison of Baseline Characteristics by Hospital Mortality Survival Status

Variables	Survival N=2685	Non-Survival N=850	P-value
Age, year	55.7 ± 15.4	58.8 ± 14.9	<0.001
Gender, Male n (%)	1746 (65.0%)	571 (67.2%)	0.268
Married, n (%)	2543 (94.7%)	810 (95.3%)	0.561
Ethnicity, n(%)			0.001
Han	1544 (57.5%)	437 (51.4%)	

Variables	Survival N=2685	Non-Survival N=850	P-value
Zangzu	103 (3.84%)	23 (2.71%)	
other	1038 (38.7%)	390 (45.9%)	
Severity score			
Apache II (onset shock), (IQR)	25.0 [21.0;28.0]	29.0 [26.0; 32.0]	<0.001
Apache II (ICU first day), (IQR)	25.0 [21.0;28.0]	29.0 [26.0; 32.0]	<0.001
SOFA (onset shock), (IQR)	11.0 [9.00;12.0]	11.0 [9.00;12.0]	0.153
SOFA (ICU first day), (IQR)	11.0 [10.0; 12.0]	13.0 [11.0; 14.0]	<0.001
Outcome			
Weekend transfer to ICU, n(%)	621 (23.1%)	196 (23.1%)	1.000
Shock duration time, hours	34.8 ± 26.9	54.7 ± 31.3	<0.001
Pre-ICU shock time, hours	3.62 ± 11.1	10.6 ± 18.0	<0.001
Pos-ICU shock time, hours	31.2 ± 23.0	44.1 ± 23.4	<0.001
Group.			<0.001
Pre-ICU time<3h	2336 (87.0%)	513 (60.4%)	
Pre-ICU time:3-6h	89 (3.31%)	61 (7.18%)	
Pre-ICU time>6h	260 (9.68%)	276 (32.5%)	
Group.			<0.001
Pre-ICU time<=6h	2425 (90.3%)	574 (67.5%)	
Pre-ICU time>6h	260 (9.68%)	276 (32.5%)	
Hospital stay time, days	15.8 [10.9; 25.8]	13.0 [6.51; 24.0]	<0.001
ICU stay time, days	3.98 [2.26; 7.49]	5.98 [2.48; 14.0]	<0.001
Type shock			
Cardiac shock, n (%)	73 (2.72%)	50 (5.88%)	<0.001
Hypovolemic shock, n (%)	825 (30.7%)	274 (32.2%)	0.432
Obstructive shock, n (%)	88 (3.28%)	10 (1.18%)	0.002
Distributive shock, n (%)	1769 (65.9%)	623 (73.3%)	<0.001
Septic shock, n(%)	1668 (62.1%)	614 (72.2%)	<0.001
Hemorrhagic shock, n (%)	340 (12.7%)	189 (22.2%)	<0.001
Anaphylactic shock, n (%)	8 (0.30%)	0 (0.00%)	0.211
Comorbidity			
CPR, n (%)	19 (0.71%)	70 (8.24%)	<0.001
Respiratory failure, n (%)	266 (9.91%)	384 (45.2%)	<0.001
Pneumonia, n (%)	1243 (46.3%)	639 (75.2%)	<0.001
Circulatory disturbance, n (%)	169 (6.29%)	206 (24.2%)	<0.001

Variables	Survival N=2685	Non-Survival N=850	P-value
Acute pancreatitis, n (%)	579 (21.6%)	239 (28.1%)	<0.001
Central nervous system disease, n (%)	171 (6.37%)	107 (12.6%)	<0.001
Kidney failure, n (%)	308 (11.5%)	306 (36.0%)	<0.001
Diabetes, n (%)	421 (15.7%)	165 (19.4%)	0.013
Liver failure, n(%)	625 (23.3%)	371 (43.6%)	<0.001
Vital signs			
DBP, (mmHg)	52.7 ± 7.71	50.3 ± 9.69	<0.001
SBP, (mmHg)	96.6 ± 15.3	92.4 ± 16.9	<0.001
MBP, (mmHg)	68.1 ± 9.36	64.9 ± 11.4	<0.001
Respiratory rate ,$(min)^{-1}$	21.6 ± 4.11	22.1 ± 5.16	0.008
Temperature, (C)	37.4 ± 0.77	37.6 ± 1.06	<0.001
Heart rate, $(min)^{-1}$	108 ± 19.3	121 ± 27.0	<0.001
Laboratory Test			
AST/ALT ratio	1.85 ± 1.05	2.25 ± 1.82	<0.001
C-reaction protein, (mg/L)	79.1 ± 83.1	112 ± 102	<0.001
eGFR, (ml/min)	92.3 ± 28.3	72.4 ± 36.1	<0.001
INR	1.43 ± 0.46	1.77 ± 1.03	<0.001
MB, (U/L)	6.94 ± 17.5	15.9 ± 41.5	<0.001
PaCO2, (mmHg)	42.2 ± 6.45	45.7 ± 11.5	<0.001
RBC, (g/L)	3.47 ± 0.71	3.32 ± 0.82	<0.001
Albumin	34.3 ± 6.30	33.1 ± 6.29	<0.001
WBC, $(\times 10^9/L)$	13.5 ± 6.70	14.1 ± 8.72	0.048
Monocyte absolute	0.76 ± 0.48	0.71 ± 0.56	0.014
TnT, (ng/L)	68.8 ± 261	186 ± 538	<0.001
K, (mmol/L)	3.47 ± 0.71	3.32 ± 0.82	<0.001
Lactate, (mmol/L)	3.49 ± 2.76	5.65 ± 5.00	<0.001
Lymphocyte, $(\times 10^9/L)$	1.12 ± 0.86	0.96 ± 0.76	<0.001
Na, (mmol/L)	143 ± 4.72	146 ± 6.66	<0.001
BUN, (mmol/L)	7.49 ± 4.94	12.5 ± 8.82	<0.001
PPT,(s)	19.7 ± 8.55	21.1 ± 10.9	0.001
Glucose, (mmol/L)	10.6 ± 3.61	11.2 ± 4.03	<0.001
Hemoglobin, (g/L)	104 ± 20.2	99.8 ± 23.4	<0.001
Platelet ,$(\times 10^9/L)$	162 ± 103	126 ± 89.9	<0.001
AG (mmol/L)	18.9 ± 4.29	22.3 ± 7.61	<0.001

Variables	Survival N=2685	Non-Survival N=850	P-value
Cr ,(μmol/L)	95.5 ± 82.1	159 ± 136	<0.001
FiO2, (%)	44.2 ± 9.71	52.6 ± 15.0	<0.001
SPO2, (%)	97.9 ± 4.30	96.3 ± 6.23	<0.001
PaO2, (mmol/L)	95.5 ± 32.6	78.5 ± 36.2	<0.001
PaO2/FiO2 ratio	226 ± 89.3	165 ± 92.6	<0.001
platelet 24h ,($\times 10^9$ /L)	144 ± 97.2	108 ± 84.9	<0.001
platelet 48h ,($\times 10^9$ /L)	125 ± 88.8	89.5 ± 71.6	<0.001
platelet 72h ,($\times 10^9$ /L)	127 ± 88.6	88.2 ± 72.6	<0.001
Cr 24h ,(μmol/L)	90.1 ± 78.8	148 ± 133	<0.001
Cr 48h ,(μmol/L)	88.1 ± 61.5	137 ± 100	<0.001
Cr 72h ,(μmol/L)	84.9 ± 66.3	120 ± 89.9	<0.001
Albumin 24h	27.9 ± 7.81	26.3 ± 7.31	<0.001
Albumin 48h	34.6 ± 4.83	33.5 ± 5.01	<0.001
Albumin 72h	34.8 ± 4.71	33.9 ± 4.86	<0.001
Hemoglobin 24h, (g/L)	96.0 ± 22.9	90.3 ± 26.0	<0.001
Hemoglobin 48h, (g/L)	88.1 ± 18.5	86.6 ± 20.4	0.107
Hemoglobin 72h, (g/L)	88.7 ± 17.8	84.8 ± 18.6	<0.001
Treatment and intervention			
Antibiotic shock 6h	828 (30.8%)	161 (18.9%)	<0.001
Antibiotic ICU 6h	855 (31.8%)	190 (22.4%)	<0.001
Total Ventilator time	90.7 ± 184	229 ± 255	<0.001
Total NE shock	24.9 ± 56.9	101 ± 135	<0.001
Total NE pre-ICU	0.00 ± 0.00	0.00 ± 0.14	0.318
Total NE post-ICU	25.8 ± 60.6	104 ± 139	<0.001
Ultrasound shock 6h	176 (6.55%)	34 (4.00%)	0.008
Ultrasound ICU 24h	1106 (41.2%)	365 (42.9%)	0.389

Note: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; DBP, Diastolic Blood Pressure; SBP. Diastolic Blood Pressure; SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; eGFR, estimated Glomerular Filtration Rate; MB, serum myoglobin; INR, International Normalized Ratio; TnT, Troponin T; PPT, Partial Prothrombin Time; AG, Anion Gap; CPR. Cardiopulmonary Resuscitation; RBC, Red Blood Cells; WBC, white blood cells; Na, Sodium; K, Potassium; Cr, Creatinine; IQR, Interquartile Range.

1.5 Survival Analysis

Survival outcomes were assessed among the three patient groups using Kaplan-Meier survival analysis curves. The analysis revealed the following:

Kaplan-Meier Curves Comparison: The survival curves indicated that patients in Groups 2 and 3 exhibited significantly lower survival rates at both 28 and 60 days compared to those in Group 1. The log-rank test confirmed these differences with a p-value of <0.001, highlighting the detrimental effect of longer pre-ICU shock times on survival.

Further Categorization: Patients were also categorized into two broader groups based on pre-ICU shock time: Group 1 (pre-ICU shock time ≤ 6 hours) and Group 2 (pre-ICU shock time > 6 hours). The Kaplan-Meier survival analysis demonstrated that patients in Group 2 had significantly lower survival rates at both 28 and 60 days compared to those in Group 1. The log-rank test confirmed these differences with a p-value of <0.001, reinforcing the critical importance of early intervention.

The results from the Kaplan-Meier curves underscore the significant impact of timely ICU transfer on patient survival. See Figure 1-9 for detailed survival curves and statistical comparisons.

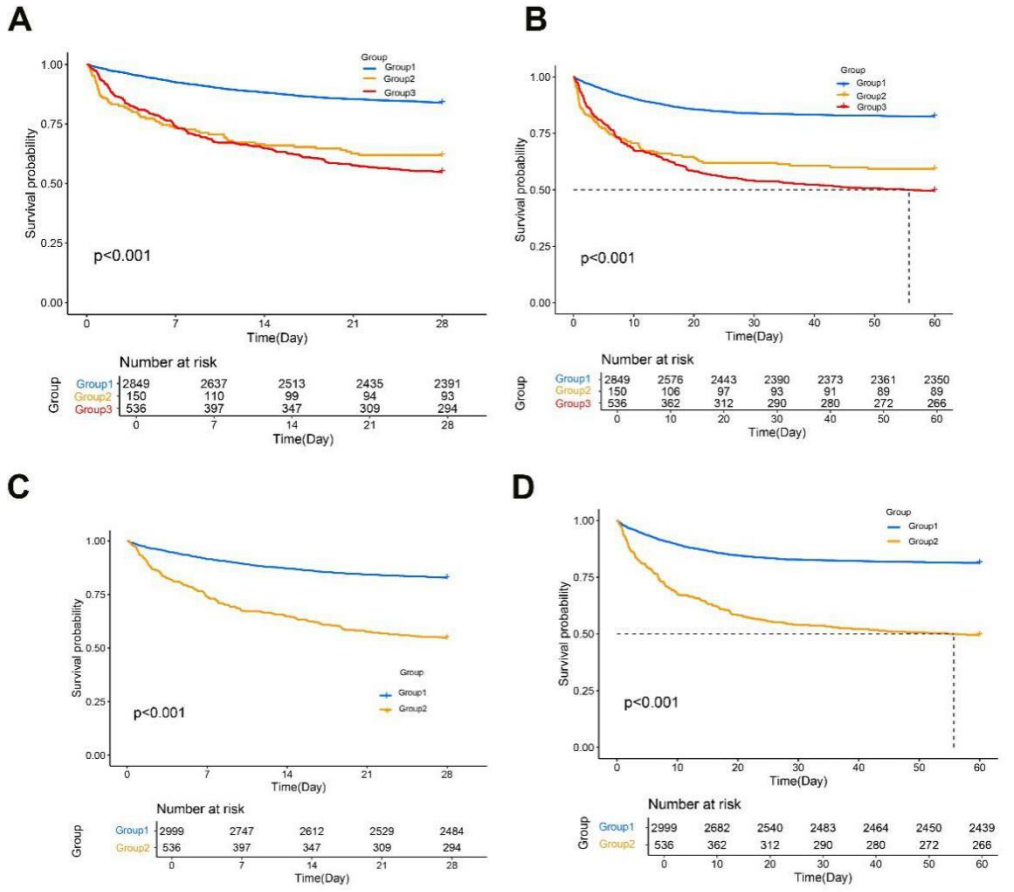


Figure 1-9: Kaplan-Meier Curves for 28-Day and 60-Day Mortality by Pre-ICU Shock Time Subgroups.

Note: (A-B) Kaplan-Meier curves comparing three pre-ICU shock time groups: <3 hours, 3-6 hours, and >6 hours, for both 28-day and 60-day mortality. Note C-D) Kaplan-Meier curves comparing two pre-ICU shock time groups: <6 hours, and ≥6 hours, for both 28-day and 60-day mortality.

1.6 Relationship Between Pre-ICU Shock Time and Clinical Outcome of Patients with Shock

1.6.1Univariate and Multivariate Logistic Regression Analysis

To elucidate the independent impact of pre-ICU shock time on mortality, logistic regression models were employed to examine its relationship with in-hospital and 28-day mortality. The analysis considered pre-ICU shock time both as a continuous and categorical variable (see Table 1-15 and Figure 1-10 for details).

Table 1-15: Univariate and multivariate logistic regression analyses were conducted to examine the relationship between pre-ICU shock time and the prognosis of patients with shock.

Categories	Univariate Model		Multivariable Model					
			Model 1		Model 2		Model 3	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Hospital mortality								
Continuous variable of pre-ICU shock time								
Pre-ICU shock time	1.033 (1.03-1.04)	<0.001*	1.025 (1.02-1.03)	<0.001*	1.025 (1.02-1.03)	<0.001*	1.023 (1.02-1.03)	<0.001*
Classification variable of pre-ICU shock time								
Group1	Reference		Reference		Reference		Reference	
Group2	3.12 (2.21-4.37)	<0.001*	2.34 (1.62-3.38)	<0.001*	2.32 (1.53-3.42)	<0.001*	2.21 (1.48-3.26)	<0.001*
Group3	4.83 (3.98-5.87)	<0.001*	3.27 (2.65-4.03)	<0.001*	3.05 (2.43-3.84)	<0.001*	2.74 (2.17-3.47)	<0.001*
28-day ICU mortality								
Continuous variable of pre-ICU shock time								
Pre-ICU shock time	1.03 (1.02-1.03)	<0.001*	1.022 (1.02-1.03)	<0.001*	1.021 (1.02-1.03)	<0.001*	1.01 (1.01-1.03)	<0.001*
Classification variable of pre-ICU shock time								
Group1	Reference							
Group2	3.20 (2.26-4.50)	<0.001*	2.40 (1.65-3.47)	<0.001*	2.37 (1.59-3.51)	<0.001*	2.23 (1.48-3.32)	<0.001*
Group3	4.30 (3.53-5.23)	<0.001*	2.84 (2.30-3.52)	<0.001*	2.61 (2.07-3.30)	<0.001*	2.31 (1.82-2.93)	<0.001*

Notes: The relationship between pre-ICU shock time and hospital mortality and 28-day ICU mortality was analyzed using logistic regression models. Model 1 was adjusted by: Age, APACHE II score, and SOFA score. Model 2 was adjusted by: All variables in Model 1, plus MAP, Lactate, Platelet, C-reaction, Cretinine, INR, PaCO2, TnT, Potassium, Sodium, PPT, Hemoglobin, and AG. Model 3 was adjusted by: All variables in Model 2, plus Renal failure, MODS, Antibiotic after shock 6 hours, and using ultrasound within the first 6 hours after shock onset.* Statistical significance (P<0.05).

Abbreviations: ICU, Intensive Care Unit; CI, Confidence Interval; OR, Odds Ratio; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; MAP, Mean Arterial Pressure; INR, International Normalized Ratio; TnT, Troponin T; PPT, Partial Prothrombin Sequential Organ Failure Assessment; MAP, Mean Arterial Pressure; INR, International Normalized Ratio; TnT, Troponin T; PPT, Partial Prothrombin Troponin T; PPT, Partial Prothrombin Time; AG, Anion Gap.

Continuous Variable Analysis:

Hospital mortality Risk:

Univariate Logistic Regression: This analysis revealed that pre-ICU shock time is a significant risk factor for in-hospital mortality, with an odds ratio (OR) greater than 1 ($OR > 1$, $P < 0.001$).

Multivariate Logistic Regression: The results across three progressively adjusted models consistently demonstrated that pre-ICU shock time remains a significant risk factor for in-hospital mortality. Specifically:

Model 1: OR = 1.025, 95% CI: 1.02-1.03, $P < 0.001$

Model 2: OR = 1.025, 95% CI: 1.02-1.03, $P < 0.001$

Model 3: OR = 1.023, 95% CI: 1.02-1.03, $P < 0.001$

28-Day ICU Mortality Risk: Similar findings were observed for 28-day mortality, with the multivariate logistic regression analysis adjusted for model 3 showing an OR of 1.01 (95% CI: 1.01-1.03), indicating that pre-ICU shock time is a significant independent risk factor for predicting 28-day mortality.

Categorical Variable Analysis:

Univariate Logistic Regression: When categorized, pre-ICU shock time demonstrated an increasing mortality risk with longer times before ICU admission. Compared to Group 1, Group 2 had an OR of 3.12 (95% CI: 2.21-4.37), and Group 3 had an OR of 4.83 (95% CI: 3.98-5.87) for in-hospital mortality.

Multivariate Logistic Regression: After adjusting for potential confounders in three models, these associations remained statistically significant:

Group 2: OR = 2.21 (95% CI: 1.48-3.26)

Group 3: OR = 2.74 (95% CI: 2.17-3.47)

28-Day ICU Mortality Analysis: For 28-day ICU mortality, the results were consistent:

Group 2: OR = 2.23 (95% CI: 1.48-3.32)

Group 3: OR = 2.31 (95% CI: 1.82-2.93) Using Group 1 as the reference, these findings underline that longer pre-ICU shock times are strongly associated with higher mortality rates.

These analyses collectively underscore the significant role of pre-ICU shock time as an independent predictor of both in-hospital and 28-day mortality, highlighting the critical importance of timely intervention in shock management.

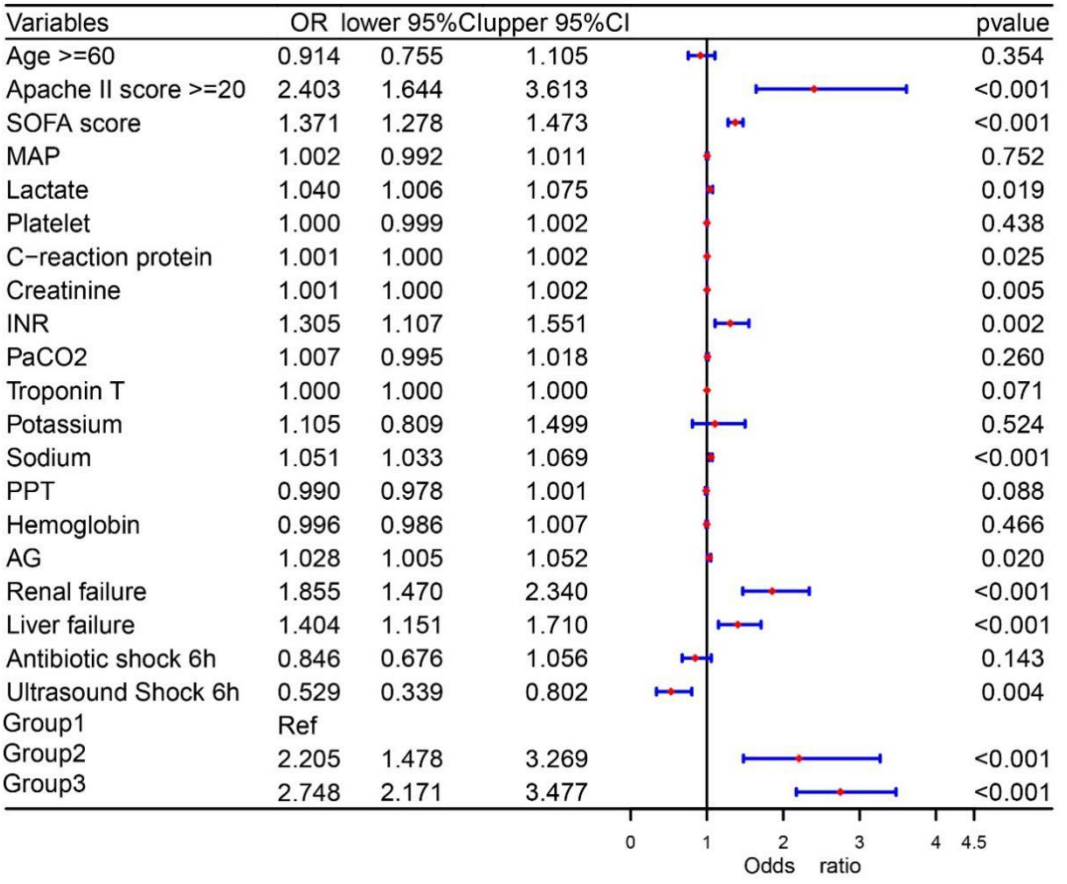


Figure 1-10: Forest Plot of Multivariate Logistic Regression Analysis For Hospital Mortality Risk Factors.

Note: Multivariate logistic regression analysis identified Apache II score ≥20, SOFA score, lactate, C-reactive protein, creatinine, INR, sodium, anion gap (AG), renal failure, liver failure, Group 2, and Group 3 as independent risk factors for in-hospital mortality. anion gap (AG), renal failure, liver failure, Group 2, and Group 3 as independent risk factors for in-hospital mortality. Additionally, the use of Additionally, the use of ultrasound within 6 hours of shock onset was associated with a protective effect on in-hospital mortality.

1.6.2 RCS regression analysis

To better understand the relationship between pre-ICU shock time and the risk of

in-hospital mortality, we employed the restricted cubic spline (RCS) regression model. Our analysis revealed a nonlinear increasing trend in the risk of in-hospital death as pre-ICU shock time lengthened. This indicates that while the overall risk does increase with longer Pre-ICU shock times, the rate of this increase varies over time. The statistical analysis confirmed a significant nonlinear relationship (P non-linearity = 0.89). This nonlinear trend is illustrated in Figure 1-11.

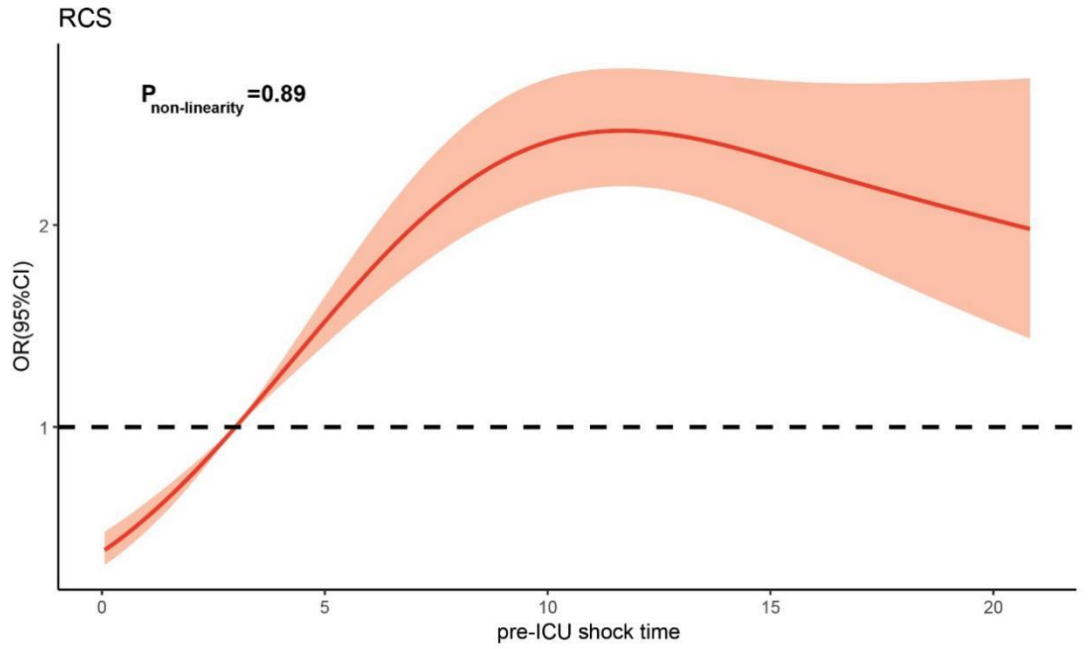


Figure 1-11: Correlation Between Pre-ICU Shock Time and Hospital Mortality of Patients with Shock.

1.6.3 Predictive Value of Pre-ICU Shock Time for Mortality Risk

We further evaluated the predictive capability of Pre-ICU shock time as a continuous variable for both in-hospital mortality and 28-day mortality using ROC curves. The analysis demonstrated that the AUC for predicting in-hospital death was 0.684 (95% CI: 0.663-0.706), while the AUC for predicting 28-day death was 0.674 (95% CI: 0.651-0.696). Similar results were observed for the predictive value of pre-ICU shock time in different shock types regarding hospital mortality risk. These findings indicate that Pre-ICU shock time is a robust predictor of mortality risk.

Detailed results are presented in Figure 1-12.

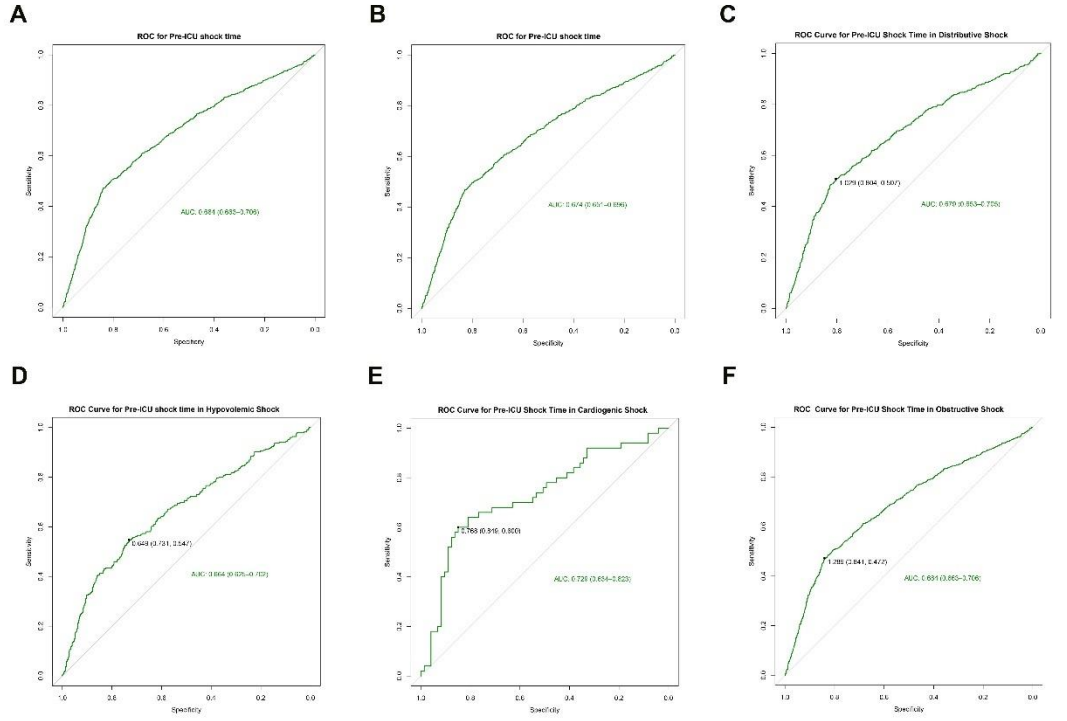


Figure 1-12: Receiver Operating Characteristic (ROC) Curve Analysis of Pre-ICU Shock Time for Predicting Hospital and 28-Day Mortality Risk.

Note: (A): ROC curve analysis for pre-ICU shock time in predicting hospital mortality. The AUC was 0.684 (95% CI: 0.663-0.706); (B): ROC curve analysis for pre-ICU shock time in predicting 28-day mortality. curve analysis for pre-ICU shock time in predicting 28-day mortality. The AUC was 0.674 (95% CI: 0.651-0.696); (C) ROC curve analysis for pre-ICU shock time in distributive shock predicting hospital mortality. The AUC was 0.679 (95% CI: 0.653-0.705); (D) ROC curve analysis for pre-ICU shock time in hypovolemic shock predicting hospital mortality. The AUC was 0.664 (95% CI: 0.625-0.702); (E) ROC curve analysis for pre-ICU shock time in cardiogenic shock in predicting hospital mortality. The AUC was 0.729 (95% CI: 0.634-0.823); (F) ROC curve analysis for pre-ICU shock time in obstructive shock predicting hospital mortality. The AUC was 0.684 (95% CI: 0.663-0.706).

1.7 Relationship Between Early Using Ultrasound and Clinical Outcome of Patients with Shock

1.7.1 Impact of Early Ultrasound Within 6 Hours of Shock Onset on Clinical Outcomes in Shock Patients

Table 1-16: Comparison of Early Ultrasound Use Within 6 Hours of Shock Onset and Other Clinical Prognostic Features

Variables	No ultrasound shock onset 6h N=3284	Ultrasound shock onset 6h N=251	P-value
Hospital mortality,n(%)			0.006
Survival	2476 (75.4%)	209 (83.3%)	
Non-survival	808 (24.6%)	42 (16.7%)	
ICU 28-day mortality,n(%)			0.004
Survival	2562 (78.0%)	216 (86.1%)	
Non-survival	722 (22.0%)	35 (13.9%)	
Shock time duration,h	39.9 (29.5)	34.7 (26.2)	0.003
Pre-ICU shock time,h	5.49 (13.7)	2.73 (9.12)	<0.001
Hospital stay time,day	15.4 [10.0;25.6]	14.2 [10.1;25.6]	0.553
ICU stay time,day	5.13 [2.90;9.00]	4.23 [2.16;8.72]	0.010

Table 1-16 indicates that early ultrasound use within 6 hours of shock onset is associated with shorter median ICU stay (4.23 [2.16; 8.72] days vs 5.13 [2.90; 9.00] days), reduced total shock duration (34.7 ± 26.2 hours vs 39.9 ± 29.5 hours), earlier ICU transfer (2.73 ± 9.12 hours vs 5.49 ± 13.7 hours), lower in-hospital mortality (42 patients, 16.7% vs 808 patients, 24.6%), and reduced ICU 28-day mortality (35 patients, 13.9% vs 722 patients, 22.0%) ($P<0.05$).

1.7.2 Survival Analysis

The survival curves indicated that the 28-day ICU mortality rate was significantly lower in the group that received early ultrasound-guided treatment within 6 hours of shock onset compared to the group without ultrasound use. The log-rank test confirmed these differences, with a p-value of 0.002 ($p < 0.05$), highlighting the positive impact of early ultrasound intervention on survival outcomes (Figure 1-13).

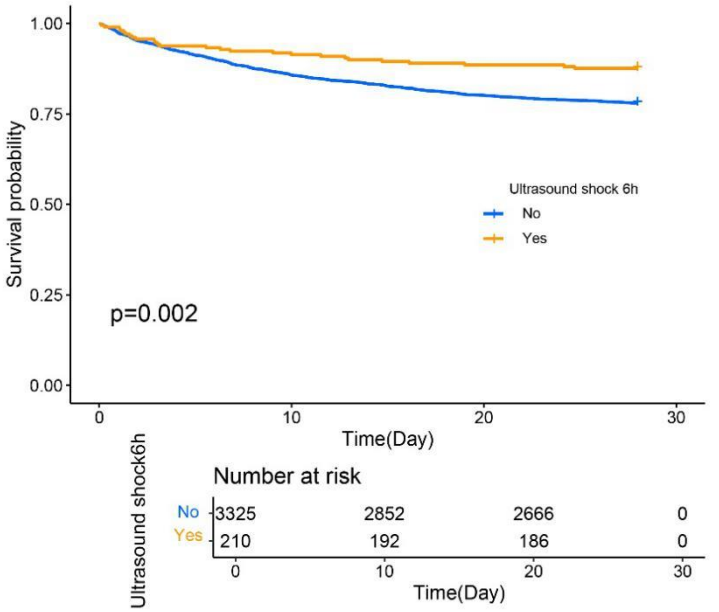


Figure 1-13: Kaplan-Meier Curves for 28-Day Mortality stratified by early ultrasound use within 6 hours of shock onset.

1.7.3 Univariate and Multivariate Logistic Regression Analysis

To elucidate the independent impact of early ultrasound use within 6 hours of shock onset on mortality, logistic regression models were employed to examine its relationship with in-hospital and 28-day mortality. The results indicated that, in univariate logistic regression analysis for in-hospital mortality, early ultrasound use within 6 hours of shock onset showed an OR < 1. In multivariate models adjusted for confounding factors, there was a trend of further reduction in the OR value, with Model 2 showing an OR = 0.48 (95%CI: 0.31–0.75, P<0.05). Similar results were observed for 28-day mortality, indicating that early ultrasound use within 6 hours of shock onset is an independent protective factor for prognosis (Table 1-17).

Table 1-17: Univariate and Multivariate Logistic Regression Analyses Examining the Association Between Early Ultrasound-Guided Treatment Within 6 Hours of Shock Onset and Patient Prognosis.

Characteristics	Univariate Model		Multivariable Model					
			Model 1		Model 2		Model 3	
	OR(95%CI)	P value	OR(95%CI)	P value	OR(95%CI)	P value	OR(95%CI)	P value
Hospital mortality								
Ultrasound within 6 hours after the onset of shock								
No	Reference		Reference		Reference		Reference	
Yes	0.59(0.40-0.85)	0.006	0.57(0.37-0.84)	0.006	0.51(0.33-0.76)	0.002	0.48(0.31-0.75)	0.001
28-day ICU mortality								
Ultrasound within 6 hours after the onset of shock								
No	Reference		Reference		Reference		Reference	
Yes	0.50(0.32-0.75)	0.001	0.47(0.30-0.72)	<0.001	0.42(0.26-0.65)	<0.001	0.39(0.24-0.62)	<0.001

Notes: The relationship between early ultrasound-guided treatment within 6 hours of shock onset and hospital mortality and 28-day ICU mortality was analyzed using logistic regression models. Model 1 was adjusted by: Age, APACHE II score, and SOFA score. Model 2 was adjusted by: All variables in Model 1, plus MAP, Lactate, Platelet, C-reaction, Cretinine, INR, PaCO2, TnT, Potassium, Sodium, PPT, Hemoglobin, and AG. Model 3 was adjusted by: All variables in Model 2, plus Renal failure, MODS, and antibiotic after shock 6 hours.* Statistical significance (P<0.05).

Abbreviations: ICU, Intensive Care Unit; CI, Confidence Interval; OR, Odds Ratio; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; MAP, Mean Arterial Pressure; INR, International Normalized Ratio; TnT, Troponin T; PPT, Partial Prothrombin Sequential Organ Failure Assessment; MAP, Mean Arterial Pressure; INR, International Normalized Ratio; TnT, Troponin T; PPT, Partial Prothrombin Troponin T; PPT, Partial Prothrombin Time; AG, Anion Gap.

1.8 Establishing a Predictive Model for In-Hospital Mortality in Shock Patients

1.8.1 Logistic Regression Analysis

Table 1-18: Univariate logistic regression analysis results for factors influencing hospital mortality in shock patients.

Variables	Estimate	OR	Lower95%CI	Upper95%CI	P-value
Age	0.013	1.013	1.008	1.019	<0.001
Gender	0.096	1.101	0.935	1.298	0.250
Married	0.123	1.131	0.797	1.640	0.503
APACHE score	0.208	1.232	1.207	1.257	<0.001
SOFA score	0.531	1.701	1.613	1.796	<0.001
Weekend	-0.004	0.996	0.828	1.194	0.967
Respiratory failure Yes	2.014	7.494	6.232	9.026	<0.001
Pneumonia Yes	1.257	3.513	2.959	4.185	<0.001
Pancreatitis Yes	0.353	1.423	1.192	1.694	<0.001
Kidney failure Yes	1.468	4.341	3.614	5.217	<0.001
Diabetes Yes	0.259	1.295	1.059	1.578	0.011
Liver failure Yes	0.937	2.553	2.170	3.003	<0.001
AST/ALT ratio	0.220	1.246	1.172	1.329	<0.001
C-reaction protein	0.004	1.004	1.003	1.005	<0.001
INR	0.801	2.228	1.944	2.568	<0.001
MB	0.012	1.012	1.009	1.016	<0.001
RBC	-0.290	0.749	0.670	0.835	<0.001
Albumin	-0.030	0.971	0.959	0.983	<0.001
WBC	0.012	1.012	1.001	1.022	0.024
TnT	0.001	1.001	1.001	1.002	<0.001
Lactate	0.148	1.159	1.136	1.184	<0.001
Lymphocyte	-0.268	0.765	0.682	0.852	<0.001
Sodium	0.100	1.105	1.089	1.122	<0.001
PPT	0.014	1.014	1.007	1.022	<0.001
Glucose	0.043	1.044	1.024	1.065	<0.001
Hemoglobin	-0.010	0.990	0.987	0.994	<0.001
Platelet	-0.004	0.996	0.995	0.997	<0.001
SpO2	-0.212	0.809	0.752	0.867	<0.001
PaO2	-0.001	0.999	0.997	1.000	<0.001
AG	0.105	1.111	1.095	1.127	<0.001
Creatinine	0.006	1.006	1.005	1.007	<0.001
MAP	-0.031	0.969	0.962	0.977	<0.001
HR	0.026	1.026	1.022	1.030	<0.001
PaO2/FiO2 ratio	-0.008	0.992	0.991	0.993	<0.001
Antibiotic shock6Yes	-0.646	0.524	0.432	0.632	<0.001
Ultrasoundshock6hYes	-0.521	0.594	0.402	0.853	<0.001
Pre-ICU shock	0.032	1.033	1.027	1.038	<0.001

To develop a model for predicting the risk of in-hospital mortality in shock patients, we first conducted univariate logistic regression analyses. All variables with a P value less than 0.05 were included in the multivariate logistic regression model. The results are presented in Table 1-18.

In the multivariate analysis, the results indicated that the Apache II score, SOFA score, respiratory failure, pneumonia, kidney failure, INR, blood lactate levels, serum sodium concentration, anion gap, PaO_2, and pre-ICU shock time were independent risk factors for in-hospital mortality among shock patients ($P < 0.05$). Conversely, serum albumin levels, lymphocyte count, PaO_2/FiO_2 ratio, and undergoing ultrasound examination within 6 hours after shock onset were independent protective factors against in-hospital mortality (all $P < 0.05$, see Figure 1-14).

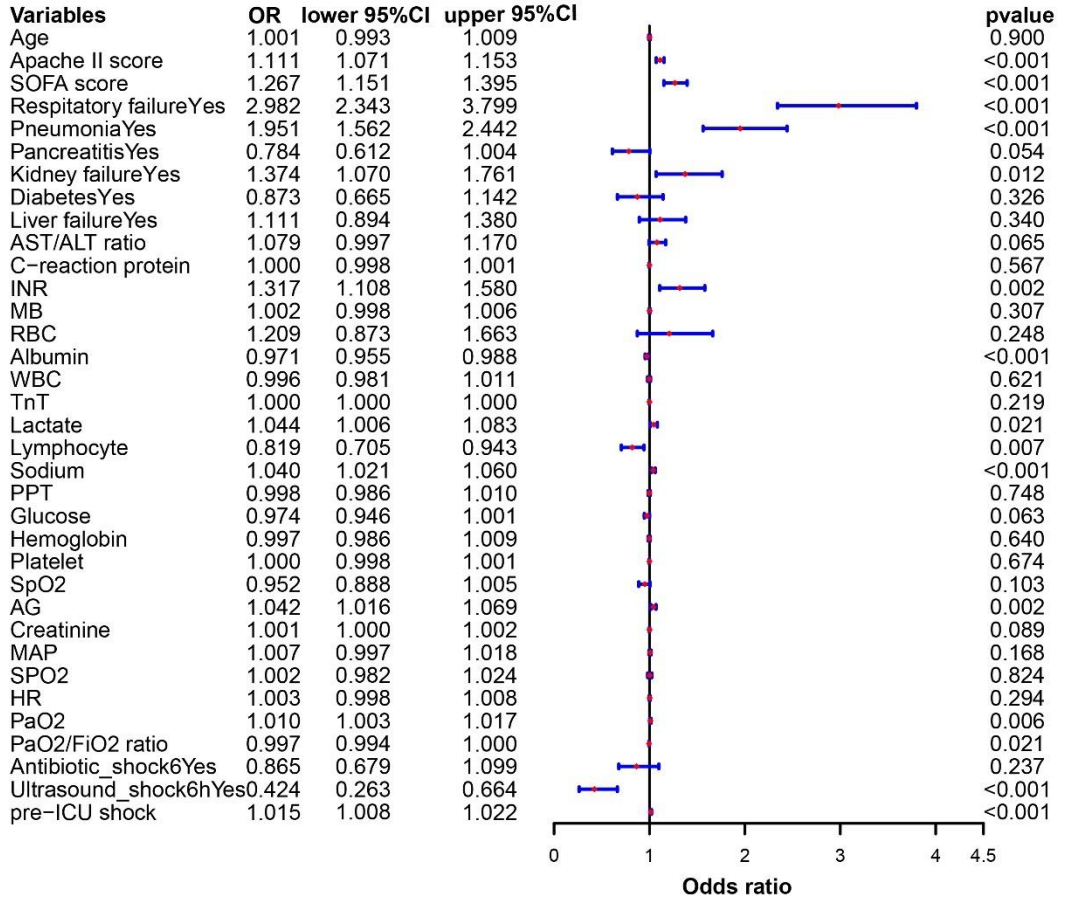


Figure 1-14: Forest Plot of Multivariate Logistic Regression Analysis for Hospital Mortality Risk Factors.

1.8.2 Model Evaluation

The in-hospital mortality risk prediction model established in this study demonstrated good discrimination and calibration. The area under the receiver operating characteristic curve (AUC) for the model in the training group was 0.855 (95% CI: 0.84–0.87), indicating high discriminatory ability. The Hosmer-Lemeshow test showed a chi-square value of 4.08 with a P value of 0.85, suggesting good calibration of the model. The calibration curve further showed a high degree of agreement between predicted probabilities and actual observed outcomes. Decision curve analysis (DCA) indicated that within a threshold probability range of 0.5–0.9, the model provided significant net benefits, supporting its use as a reliable clinical predictive tool (see Figure 1-15).

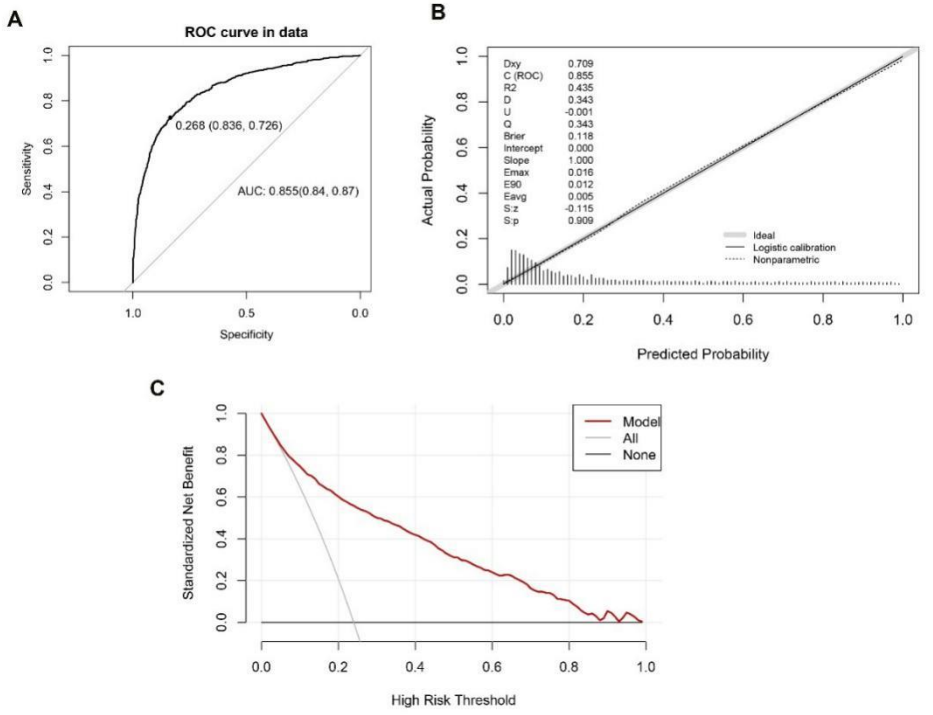


Figure 1-15: ROC, Calibration, and Decision Curve Analysis for the In-Hospital Mortality Risk Prediction Model

(A) ROC curve for the in-hospital mortality risk prediction model in shock patients.

(B) Calibration curve for the in-hospital mortality risk prediction model in shock patients.

(C) Decision curve analysis (DCA) for the in-hospital mortality risk prediction model in shock patients.

2. Prognostic Impact of a New Visualized OPACCUS Diagnostic and Therapeutic Assessment Process for Shock Based on Etiology, Hemodynamics, and Organism Response

2.1 Flow Chart Research

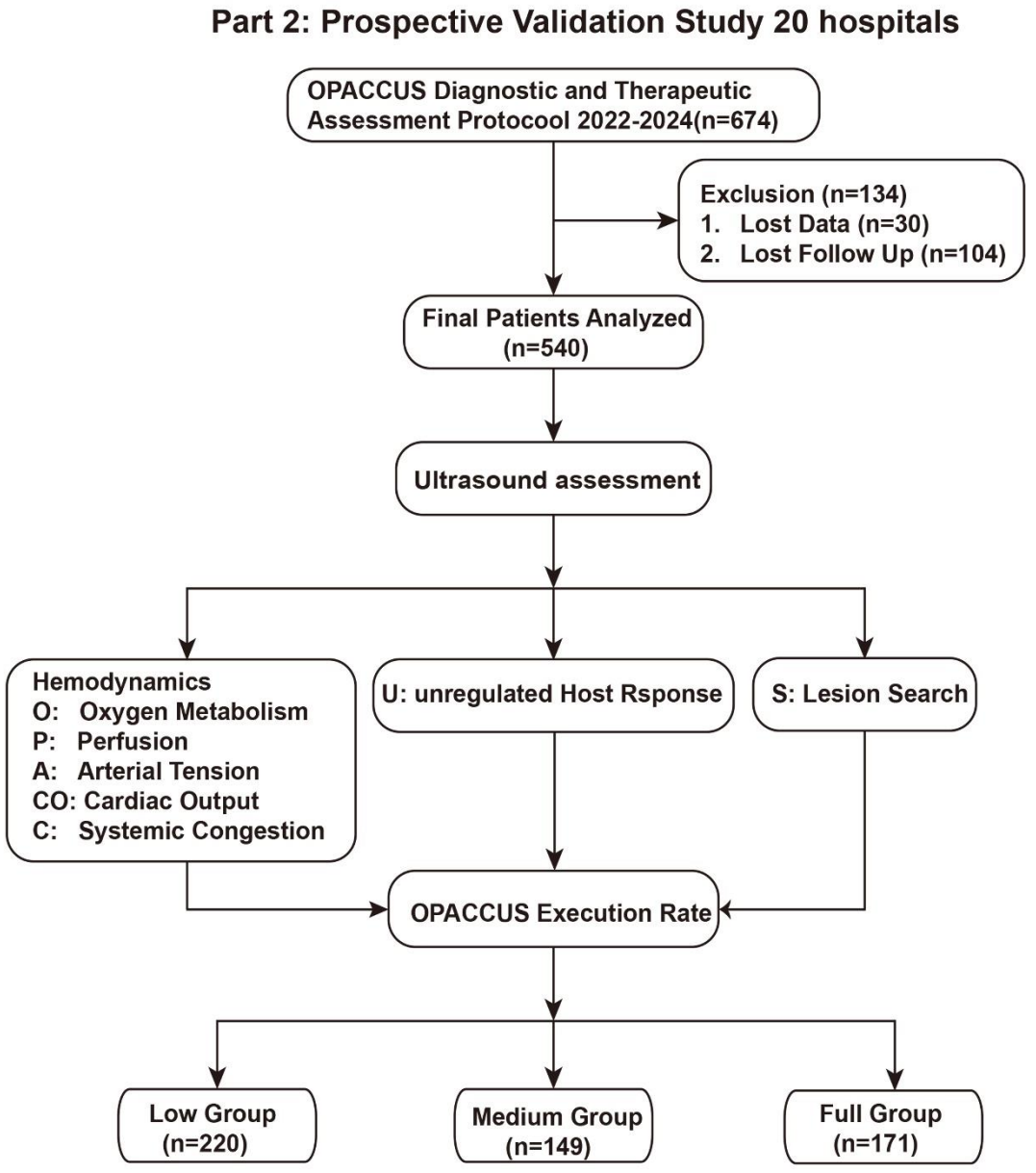


Figure 2-1: Flow chart of the Research Study population.

2.2 Enrollment and Grouping

Between October 2022 and February 2024, a total of 674 patients were enrolled. After excluding 30 patients due to data loss and 104 patients who were lost to follow-up, 540 patients were included in the final analysis.

The average age of the patients was 58 ± 17 years. The cohort comprised 185 males (34.26%) and 355 females (65.74%). The distribution of patient types was as follows: acute respiratory and circulatory compromise (368 patients, 68.15%), multiple system organ failure (163 patients, 30.19%), and postoperative monitoring (9 patients, 1.67%). Additionally, 66 patients (12.22%) underwent continuous renal replacement therapy (CRRT).

At the time of enrollment, the average APACHE II score was 19.95 ± 8.38, and the mean SOFA score was 7.10±2.52.

Patients were classified into three groups based on OPACCUS execution rate, using tertiles to define the groups:

- Full Group (n=171, OPACCUS execution rate = 100%)
- Medium Group (n=149, 50% ≤ OPACCUS execution rate < 100%)
- Low Group (n=220, OPACCUS execution rate < 50%)

2.3 Baseline Characteristics

Table 2-1 presents the baseline characteristics, clinical information, and hemodynamic parameters across the three patient groups. The results show that the mean SOFA in the full execute group was 6.75 ± 2.43, which was significantly lower than that of the other groups. The mean value for the medium-execute group was 7.46 ± 2.57, while the low-execute group had the lowest mean SOFA at 7.12±2.52 ($F=3.19$, $P<0.05$). Additionally, there was a significant difference in the proportion of patients with urine volume <0.5 ml/kg.h due to prerenal or shock conditions among the groups ($\chi^2 = 21.00$, $P < 0.001$). No other indicators showed statistically significant differences.

Table 2-1: Baseline Demographic Information and Comparability Analysis of OPACCUS Groups

Variables	Overall	Low Group (n=220)	Medium Group (n=149)	Full Group (n=171)	Statistic	*P-value*
Age, years	58±17	57±17	58±18	58±17	*F*=0.39	0.680
Gender, n(%)					χ^2=3.77	0.152
Male	185(34.26)	75(34.09)	43(28.86)	67(39.18)		
Female	355(65.74)	145(65.91)	106(71.14)	104(60.82)		
BMI, kg/m^2	23.07±4.07	22.99±3.97	23.29±4.25	22.97±4.06	*F*=0.31	0.733
Severity score						
APACHEE II	19.95±8.38	20.07±7.92	19.71±8.18	20.01±9.13	*F*=0.09	0.918
SOFA	7.10±2.52	7.12±2.52	7.46±2.57	6.75±2.43	*F*=3.19	0.042*
RASS, (IQR)	4.00[3.00,4.00]	4.00[3.00,4.00]	4.00[3.00,4.00]	4.00[3.00,4.00]	*H*=1.27	0.53
Vital signs						
HR, bpm	102.31±24.53	102.41±24.03	102.65±24.85	101.89±25.03	*F*=0.04	0.960
RR, bpm	17.82±4.85	17.90±4.91	17.73±5.24	17.78±4.44	*F*=0.06	0.939
SBP, mmHg	114.06±23.33	113.17±22.45	114.30±22.18	115.01±25.43	*F*=0.31	0.735
Admission categories, n(%)						0.076
Postoperative monitoring	9(1.67)	1(0.45)	6(4.03)	2(1.17)		
Multiple system organ failure	163(30.19)	72(32.73)	44(29.53)	47(27.49)		
Acute respiratory and Circulatory compromise	368(68.15)	147(66.82)	99(66.44)	122(71.35)		
Type of Surgery, n(%)					χ^2=1.35	0.852
non	272(50.37)	115(52.27)	75(50.34)	82(47.95)		
Emergency	106(19.63)	39(17.73)	29(19.46)	38(22.22)		
Elective	162(30.00)	66(30.00)	45(30.20)	51(29.82)		

Variables	Overall	Low Group (n=220)	Medium Group (n=149)	Full Group (n=171)	Statistic	*P-value*
Mechanical ventilation, n(%)					χ^2=1.95	0.745
V-V ECMO	37(6.85)	18(8.18)	7(4.70)	12(7.02)		
Noninvasive	19(3.52)	7(3.18)	5(3.36)	7(4.09)		
Invasive	484(89.63)	195(88.64)	137(91.95)	152(88.89)		
PEEP, mmHg	7.44±2.37	7.22±2.35	7.63±2.42	7.53±2.34	*F*=1.55	0.213
PI/PS	12.13±3.95	11.70±3.54	12.36±4.44	12.50±3.96	*F*=2.34	0.097
Actual Bicarbonate Radical, mmHg	22.10[20.00,24.30]	21.60[19.90,24.00]	21.80[19.90,24.30]	22.70[20.30,24.90]	*H*=2.20	0.332
CVP, mmHg	10.19±4.44	9.98±4.59	10.16±3.89	10.48±4.72	*F*=0.61	0.546
24h VISmax	120.23±228.26	127.58±281.79	129.39±200.49	102.79±165.70	*F*=0.73	0.481
CRT,s	2.90±1.27	2.93±1.28	2.92±1.20	2.83±1.32	*F*=0.38	0.687
Perfusion Index	0.87[0.41,1.30]	0.91[0.53,1.50]	0.81[0.36,1.20]	0.87[0.32,1.20]	*H*=5.99	0.05
Lactate ,mmol/L	2.98[2.00,5.20]	3.05[2.05,5.45]	2.80[1.90,5.20]	3.00[2.10,4.80]	*H*=1.27	0.531
pH	7.37±0.08	7.36±0.08	7.37±0.07	7.37±0.08	χ^2=5.04	0.081
ScvO2,%	69.70[57.60,75.90]	69.00[56.40,75.90]	71.50[60.00,75.90]	71.50[57.60,75.30]	*H*=0.50	0.778
GAP, mmHg	6.80[4.90,9.10]	6.90[5.40,9.00]	6.70[4.80,9.60]	6.70[4.90,9.00]	*H*=0.22	0.897
Urine volume from prerenal or shock< 0.5ml/kg·h, n(%)					χ^2=21.00	<0.001*
Unclear	49(9.07)	11(5.00)	13(8.72)	25(14.62)		
No	196(36.30)	71(32.27)	51(34.23)	74(43.27)		
Yes	295(54.63)	138(62.73)	85(57.05)	72(42.11)		
CRRT, n(%)					χ^2=1.37	0.503
Yes	66(12.22)	25(11.36)	16(10.74)	25(14.62)		
No	474(87.78)	195(88.64)	133(89.26)	146(85.38)		

Variables	Overall	Low Group (n=220)	Medium Group (n=149)	Full Group (n=171)	Statistic	*P-value*
Ultrafiltration, ml/h	76.65±74.17	72.59±70.44	80.60±80.55	78.42±73.25	*F*=0.59	0.555
PaO2, mmHg	105.80[84.60,152.00]	105.80[81.60,157.00]	102.00[85.10,143.60]	103.00[85.10,153.00]	*H*=1.53	0.466
PaCO2, mmHg	39.60[34.40,45.00]	40.20[33.90,45.00]	38.70[33.90,43.50]	39.60[35.90,43.50]	*H*=1.33	0.515
Oxygenation Index	252.60±121.02	257.20±123.51	236.46±115.30	260.74±122.02	*F*=1.88	0.154
Hb, g/L	93.80[78.40,113.55]	93.40[77.40,113.45]	93.90[79.90,113.00]	95[79.70,118.80]	*H*=0.48	0.786
TBIL (umol/L)	33.96±39.91	36.46±44.92	31.29±31.93	33.06±39.35	*F*=0.81	0.447
Creatinine (umol/L)	142.76±140.61	137.07±120.60	154.45±127.18	139.89±172.32	*F*=0.73	0.482
IL-6, ng/L	1429.27±1594.12	1268.68±1551.05	1505.04±1597.00	1569.86±1636.88	*F*=1.96	0.142
CRP, mg/L	104.00[65.20,161.00]	100.00[61.80,152.50]	103.20[65.20,148.30]	111.00[65.20,209.00]	*H*=3.28	0.194
PCT, ng/mL	34.60[17.60,55.00]	28.35[15.60,55.00]	36.00[20.20,51.70]	33.20[14.78,58.60]	*H*=1.46	0.483
Urine output per hour, ml/h	50.00[20.00,100.00]	50.00[20.00,100.00]	40.00[20.00,90.00]	50.00[20.00,100.00]	*H*=0.40	0.821
1st 24h total intake, (ml)	1600[950,2515]	1885[1039,2515]	1556[950,2410]	1556[906,2498]	*H*=4.17	0.124
1st 24h total output, (ml)	2620[1790,3758]	2644.65[1865,4001]	2450[1790,3758]	2590[1810,3419]	*H*=2.07	0.355

Note: IQR, Interquartile Range; BMI, Body Mass Index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; RASS, Richmond Agitation-Sedation Scale; DBP, Diastolic Blood Pressure; SBP, Systolic Blood Pressure; T, Body Temperature; RR, Respiratory Rate; HR, Heart Rate; CVP, Central Venous Pressure; VIS, Vasopressor Inotrope Score; CRT, Vasopressor Inotrope Score; ScvO2, Central Venous Oxygen Saturation; CRRT, Central Venous Oxygen Saturation; CRP, C-Reactive Protein; PCT, Procalcitonin; Hb, Hemoglobin; IL-6, Interleukin-6;

* denoted $P < 0.05$ among groups.

2.4 Primary Outcome Indicators and Multivariate Regression Model

Table 2-2: Comparison of 30-day Mortality Rates Among OPACCUS Groups

Variables	Overall	Low group	Medium group	Full group	P-value
30-day mortality,n(%)					0.003
Survival	380(70.37)	139(63.18)	106(71.14)	135(78.95)	
Non-survival	160(29.63)	81(36.82)	43(28.86)	36(21.05)	

This study found that among the OPACCUS groups, a total of 160 patients (29.63%) died within 30 days see Table 2-4. The full execution group had the lowest mortality rate, with 36 patients (21.05%) dying; the medium execution group had a mortality rate of 43 patients (28.86%), and the low execution group had the highest mortality rate, with 81 patients (36.82%). Although univariate analysis showed significant differences in mortality rates among the three groups, univariate and multivariate regression analyses indicated that the 30-day mortality rate in the full execution group was significantly lower than that in the low execution group [HR = 1.646, 95% CI (1.082–2.505), $P < 0.05$]. Additionally, the mortality rate in the full execution group was also lower than that in the medium execution group [HR = 1.254, 95% CI (0.783–2.009), $P > 0.05$], but the difference in mortality rates between the medium execution group and the low execution group was not statistically significant.

A multivariate regression model was constructed with the outcome at discharge as the dependent variable, the group as the independent variable, and baseline factors with statistically significant differences between groups as covariates. In the adjusted model, the difference in all-cause mortality was statistically significant when comparing the full execution group (21.05%) with the low execution group (36.82%) (HR = 1.646*, RMST = -3.223*). However, the difference was not statistically significant when comparing the full execution group (21.05%) with the medium execution group (28.86%) (HR = 1.254, RMST = -3.783). For detailed results, see Table 2-3, and Table 2-4.

Table 2-3: Multivariate Analysis of Primary and Secondary Outcomes

Variable	*Model*	*Unadjusted Model*		*Adjusted Model*	
		Low	*Medium*	*Low*	*Medium*
Primary outcome					
30day mortality	RMST *(95%CI)*	**-4.53(-8.18,-0.89)***	-3.20(-7.38,0.98)‡	**-3.22(-7.55~-1.10)***	-3.783 (-7.96~0.395)
	HR *(95%CI)*	1.397(0.922,2.117)	1.113(0.70,1.769)	**1.646(1.082~2.505)***	1.254 (0.783~2.009)†
Secondary outcome					
Microcirculatory correction time	Estimate *(95%CI)*	4.50(-0.23,9.23)	0.596(-4.62,5.82)	4.09(-0.75~8.93)	0.118(-5.18~5.42)
ICU fees		0.818(-2.903,4.539)	**5.73(1.68,9.78)***	1.351(-2.467~5.168)	**4.613(0.43~8.79)***
Hospitalization expenses		1.745(-2.632,6.112)	**5.99(1.17,10.23)***	1.31(-2.91~5.53)	**5.58(0.96~10.20)***
ICU LOS		-1.08(-5.44,3.28)	0.526(-4.29,5.34)	-1.983 (-6.397~2.43)	0.317 (-4.51~5.15)
Ventilator LOS		-1.314(-4.74,2.11)	0.134(-3.65,3.92)	-1.334(-4.51~1.84)	0.327(-3.15~3.80)

NOTE:

a. The reference group was the full execute group. Model 1 and Model 2 were adjusted by the SOFA score, urine volume due to prerenal causes or shock< 0.5 ml/kg·h, IBP/NIBP, perfusion index, pH, and CVP.

b. * denotes P<0.05 compared with the reference group.

c. † vs. the moderate execute group; the CI of the HR does not include 1, for which HR=1.659 (95% CI= 1.105~2.490). ‡Represents a low execute group compared to a moderate execute group. The RMST 95% CI does not include 0: RMST=-3.256 (-5.826, -0.685) in the unadjusted model and RMST=-3.256 (-5.907, -1.036) in the adjusted model.

d. RMST-IPCW regression offers an alternative to pseudovalue regression for fitting RMST models. The main difference is that IPCW regression assumes that the censoring distribution can be correctly estimated, whereas pseudovalue regression does not. HR is estimated using the Cox Proportional Hazards model, and an Estimate is obtained using the Generalized Linear Model (GLM).

RMST, Restricted Mean Survival Time; HR, Hazard Ratio; CI, Confidence Interval; ICU, Intensive Care Unit; LOS, Length of Stay; SBP, Systolic Blood Pressure; RR, Respiratory rate; IBP, invasive blood Pressure; NIBP, Non-Invasive Blood Pressure;

Table 2-4: Multivariate analysis of primary outcomes (RMST)

Variable	**Level**	**β**	**S.E**	χ^2	***P-value***
Intercept		-19.632	47.302	0.17	0.678
OPACCUS rate (%)	Low execute	2.520	1.243	4.11	0.043
	Moderate execute	-0.335	1.145	0.09	0.770
	Full execute	Ref (1.00)			
Urine output resulting from prerenal or shock	No	-3.429	1.136	9.11	0.003
	Yes	Ref (1.00)			
Perfusion Index		0.266	0.590	0.20	0.653
PH		3.072	6.417	0.23	0.632
CVP		0.125	0.119	1.10	0.295
SOFA		0.733	0.255	8.28	0.004

Note: Multivariate analysis: Clinically relevant baseline variables or those demonstrating a significant univariate association with the outcome measure were included in the multivariate regression model (RMST/COX/GLM). The selection of variables was more inclined to clinical experience, considering the limited number of observed events, in order to maintain the parsimony and predictive power of the final statistical model.

2.5 Survival Analysis

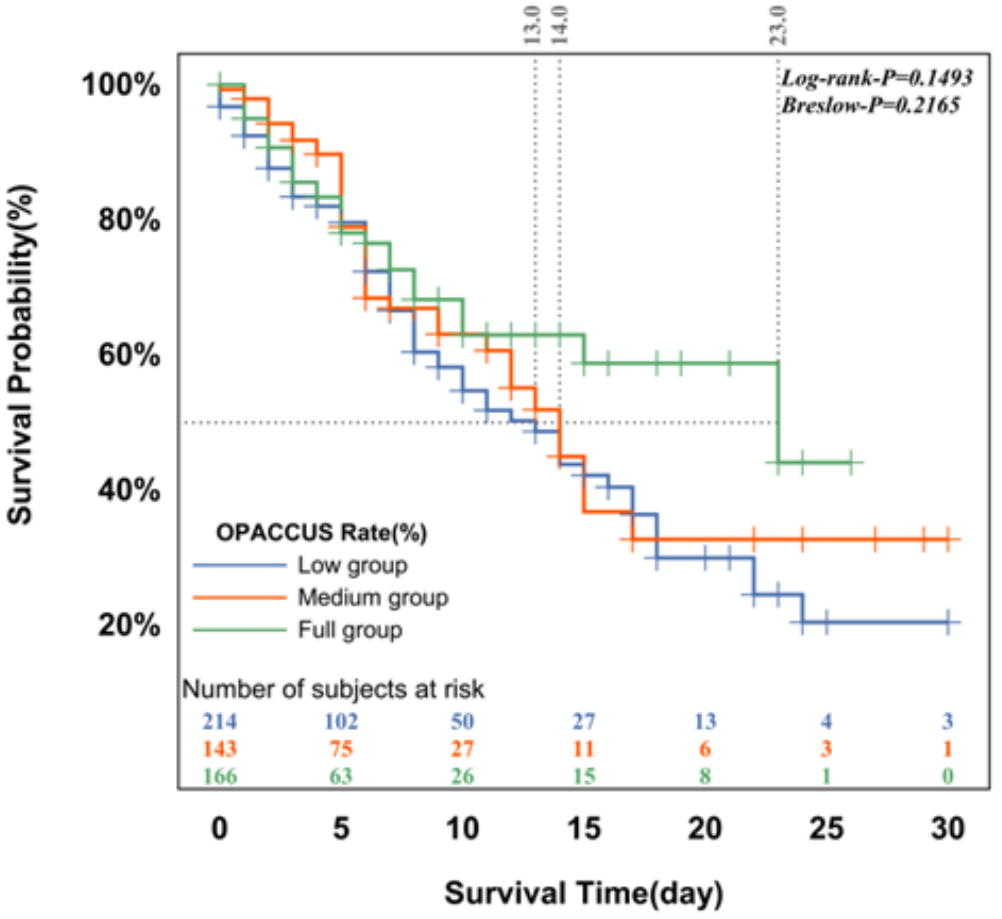


Figure 2-2: Kaplan-Meier Log-Rank Curve

The results of the Kaplan-Meier (KM) analysis (Figure 2-2) indicated a delayed effect in the KM curves among the three OPACCUS executive rate subgroups, with overlapping and crossing curves, which reduced the efficacy of the Log-rank test. Additionally, the Supremum test showed that the OPACCUS rate (%) subgroups did not satisfy the proportional hazards (PH) assumption, rendering the Log-rank test invalid. The results of the Fleming test (Table 2-5) demonstrated that there was no statistically significant difference among the three groups during the initial 30-day period. However, statistically significant differences were observed in the middle segment (P = 0.0459) and the latter segment (P = 0.0399).

Table 2-5: Fleming Test

Type of test	Weight	Z	*P*
Test early difference	Fleming (1,0)	3.1109	0.2111
Test middle difference	Fleming (1,1)	6.1608	0.0459
Test late difference	Fleming (0,1)	6.4442	0.0399
Log-rank test	Fleming (0,0)	3.8040	0.1493

Note: The Fleming test statistic Z is estimated for each of the four weight combinations of FH(p,v), FH(0,0), FH(0,1), FH(1,0), and FH(1,1), and the maximum value of Z is used as the final test conclusion, i.e., Zmax=max(|Z1|,|Z2|,|Z3|,|Z4|). The advantage of the Max-Combo test is that the Type I error is well controlled and maintains robustness to different non-proportional risk scenarios.

To further elucidate the differences between the groups, we conducted a Landmark analysis to visualize this association. The cut-off point was preliminarily determined to be around 6 days based on the KM curve. In the first segment of the Landmark analysis, there was no statistically significant difference between the three groups (Log-rank P = 0.1493), while in the second segment, there was a statistically significant difference (Log-rank P = 0.0253), as shown in Figure 2-3. However, the cut-off point for the Landmark analysis was challenging to establish, and the cumulative martingale residual plots indicated that the proportional hazards assumption was not met. To quantify the differences between the three groups, further analyses were conducted using Restricted Mean Survival Time (RMST) for both univariate and multivariate analyses.

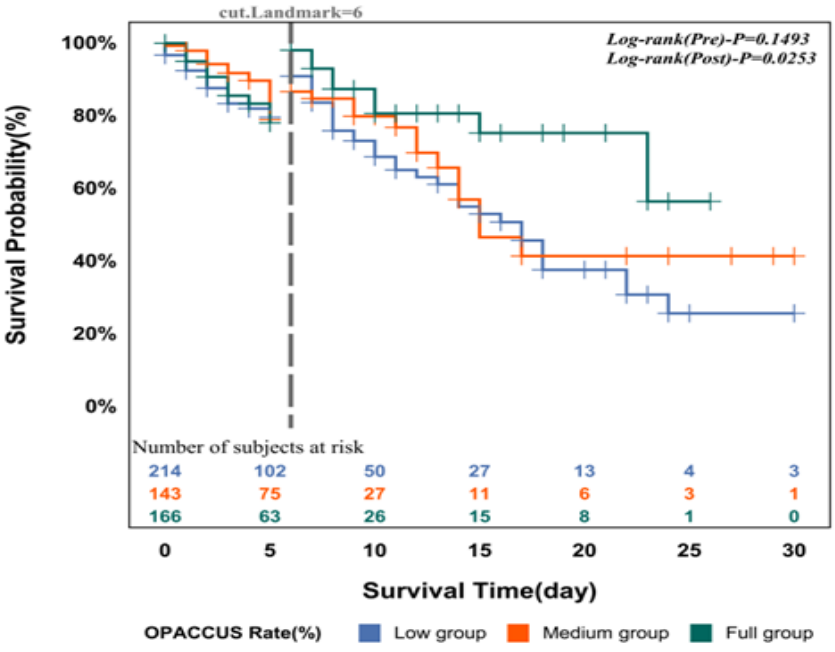


Figure 2-3: Landmark KM Curve

2.6 Restricted Mean Survival Time (RMST) analysis

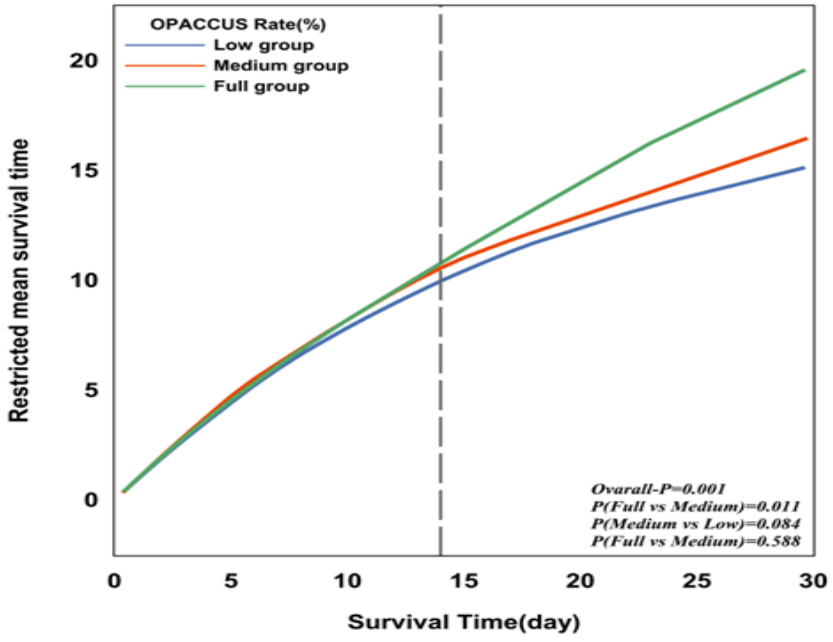


Figure 2-4: Comparison of RMST curves for three OPACCUS Execution Rate (%) Groups

Note: This figure illustrates the comparison of Restricted Mean Survival Time (RMST) curves

among three groups categorized by OPACCUS execution rates: Low Execution Group, Medium Execution Group, and High Execution Group. The figure highlights that higher OPACCUS execution rates are associated with longer survival times. The RMST curve for the High Execution Group remains higher compared to the Low Execution Group, suggesting that increased execution rates positively impact patient survival.

In this study, the Restricted Mean Survival Time (RMST) was analyzed to assess survival outcomes across three different OPACCUS execution rate groups: full execution group, medium execution group, and low execution group. The RMST curves, representing the average survival time within a specified time period, showed similar trends across the first 14 days for all groups.

Trend Analysis:

- **Initial Phase (0-14 days):** During this period, the RMST curves for all three groups showed a similar trajectory, indicating comparable survival times across the groups in the early phase of the observation.
- **Post-14 Days:** After 14 days, the trends diverged:
- **Low Execution Group:** The rate of increase in RMST began to slow down, suggesting that survival benefits in this group were not improving as rapidly.
- **Medium Execution Group:** The RMST continued to rise, but at a slower rate compared to the high execution group.
- **High Execution Group:** The RMST curve showed a steady and stable increase, indicating prolonged survival times.

This observation implies that higher OPACCUS execution rates are associated with better survival outcomes, as evidenced by the consistently higher RMST in the high execution group compared to the other groups (see Figure 2-4).

Detailed RMST Findings:

Mean RMST within 30 Days:

- **Low Execution Group:** The average RMST was 15.240 ± 1.050 days.
- **Medium Execution Group:** The average RMST was 16.572 ± 1.482 days.
- **Full Execution Group:** The average RMST was 19.774 ± 1.527 days.

The differences in RMST among these groups were statistically significant (Z =

6.992, P = 0.039), indicating that the OPACCUS execution rate significantly impacts survival time.

Pairwise Comparisons:

Low vs. Full Execution Group: The RMST was significantly lower in the low execution group compared to the full execution group, with a difference of 4.534 days (mean RMST difference: -4.534 days [95% CI: -8.176 to -0.893], P = 0.043). This suggests that patients in the low execution group had a notably shorter survival time compared to those in the full execution group.

Low vs. Medium Execution Group: The difference between the low and medium execution groups was not statistically significant (P = 0.845).

Medium vs. High Execution Group: The difference between the medium and high execution groups was also not statistically significant (P = 0.347).

Table 2-6: Univariate Analysis of RMST for OPACCUS Execution Rate Groups

Item	*Low group*	*Medium group*	*High group*	*Z*	*P-value*
RMST	15.240±1.050	16.572±1.482	19.774±1.527	6.992	0.039
RMST:(Low)-(Medium)		-1.332(-4.901,2.236)		0.538	0.845
RMST:(Low)-(High)		-4.534(-8.176,-0.893)		5.987	***0.043****
RMST:(Medium)-(High)		-3.202(-7.383,0.978)		2.265	0.347

Note: * Represents P value ≤0.05.

In the unadjusted model, the low execution group showed a survival time reduction of 4.534 days compared to the full execution group (95% CI: -7.549 to -1.103). After adjusting for confounders, the low execution group had a survival time reduction of 3.223 days compared to the high execution group (95% CI: -7.549 to -1.103). These results further validate that higher OPACCUS execution rates are associated with significantly longer survival times, underscoring the importance of OPACCUS execution rates in improving patient outcomes. See Table 2-6.

2.7 Secondary Outcome Indicators

Microcirculatory Correction Time

When comparing the microcirculatory correction times among the three groups, the Full Execution Group had the shortest median correction time of 4.50 days

(interquartile range: 2.71–7.50 days). The Medium Execution Group had a median of 5.83 days (interquartile range: 4.08–9.46 days), and the Low Execution Group had a median of 5.38 days (interquartile range: 2.83–10.63 days). However, both univariate and multivariate analyses showed that the differences in microcirculatory correction time between the three groups were not statistically significant in the 30-day mortality analysis ($P > 0.05$).

Systemic Circulation Correction time

No significant difference was found in the systemic circulation correction times among the three groups ($F = 0.36$, $P = 0.70$).

ICU Fees

Comparing ICU costs among the three groups, the Full Execution Group had the lowest median ICU cost of ¥83,800 (interquartile range: ¥50,600–¥199,100). The Medium Execution Group had a median of ¥150,700 (interquartile range: ¥71,200–¥279,400), and the Low Execution Group had a median of ¥90,800 (interquartile range: ¥39,500–¥229,800). After adjusting for 30-day mortality in a multivariate analysis, ICU costs in the Full Execution Group were significantly lower than those in the Medium Execution Group by ¥46,130 (95% CI: 0.433–8.793), with a statistically significant difference ($P < 0.05$).

Hospitalization Expenses

Hospitalization expenses showed that the Full Execution Group had the lowest median cost of ¥154,400 (interquartile range: ¥81,500–¥259,300). The Medium Execution Group had a median of ¥224,400 (interquartile range: ¥148,000–¥367,400), and the Low Execution Group had a median of ¥172,800 (interquartile range: ¥83,700–¥297,500). After a multivariate adjustment for 30-day mortality, the hospitalization costs in the Full Execution Group were significantly lower than those in the Medium Execution Group by ¥55,830 (95% CI: 0.963–10.202), with a statistically significant difference ($P < 0.05$).

ICU Length of Stay

Comparing the ICU length of stay among the three groups, the Full Execution Group had a median stay of 6 days (interquartile range: 3–14 days), the Low Execution

Group had a median stay of 7 days (interquartile range: 3–16 days), and the Medium Execution Group had the longest median stay of 9 days (interquartile range: 4–17 days). Despite the shortest ICU stay in the Full Execution Group, the differences between the groups were not statistically significant in univariate and multivariate analyses of 30-day mortality (P > 0.05).

Ventilator Length of Stay

In comparing the ventilator length of stay among the three groups, the Full Execution Group had a median of 5 days (interquartile range: 2–11 days), the Low Execution Group had a median of 6 days (interquartile range: 2–11.5 days), and the Medium Execution Group had a median of 7 days (interquartile range: 4–14 days). Although the Full Execution Group had the shortest duration of ventilator use, the differences between the groups were not statistically significant in univariate and multivariate analyses of 30-day mortality (P > 0.05).

For detailed information, see Table 2-7.

Table 2-7: Univariate Analysis of Secondary Outcome Indicators

Variable	***Low group (n=220)***	***Medium group (n=149)***	***High group (n=171)***	***Statistic***	***P-value***
Microcirculatory correction time, day	5.38[2.83,10.63]	5.83[4.08,9.46]	4.50[2.71,7.50]	*H*=8.02	**0.018***
Systemic circulation correction time, day	5.72 ± 10.00	5.28 ± 6.21	5.00 ± 8.11	*F*=0.36	0.700
ICU fees, RMB 10,000	9.08[3.95,22.98]	15.07[7.12,27.94]	8.38[5.06,19.91]	*H*=15.65	**<0.001***
Hospitalization expenses, RMB 10,000	17.28[8.37,29.75]	22.44[14.80,36.74]	15.44[8.15,25.93]	*H*=21.05	**<0.001***
ICU LOS, days	7.00[3.00,16.00]	9.00[4.00,17.00]	6.00[3.00,14.00]	*H*=8.42	**0.015***
Ventilator LOS, days	6.00[2.00,11.50]	7.00[4.00,14.00]	5.00[2.00,11.00]	*H*=9.57	**0.008***

Note: LOS, length of stay; ICU, Intensive Care Unit;

Statistical tests used: H = Kruskal-Wallis H test, F = Analysis of Variance (ANOVA).

*****Indicates statistical significance with a P value ≤0.05.

2.8 Subtypes of the Clinical Phenotype

The OPACCUS diagnostic and treatment protocol categorizes the pathophysiologic changes in the hemodynamics of shock into seven aspects: oxygen metabolism, perfusion, arterial tone/arterial resistance, cardiac output, and systemic congestion. The cause of severe disease is described as an unregulated host response, while the primary lesion is classified under lesion search. Table 2-8 summarizes the baseline clustering metrics for the OPACCUS subgroups. The results show statistically significant differences in the pathophysiologic changes related to oxygen metabolism, perfusion, arterial tone, and cardiac output ($P < 0.05$). However, no statistically significant differences were observed for systemic congestion, unregulated host response, and lesion search among the groups ($P > 0.05$).

For the subtype analysis, the LCA clustering model was used to classify OPACCUS into six shock phenotypes. Figure 2-5 visualizes the final model for each group, where the Y-axis represents the probability of an entry and the X-axis represents the entry. Table 2-9 indicates comparability among the six groups ($P < 0.05$). Additionally, Table 2-10 highlights a statistically significant difference in the comparison of LCA subgroups and patient outcomes ($P < 0.001$).

Table 2-8: Description of Baseline Clustering Metrics for OPACCUS Subgroups with Comparability Analysis

Variable	*All N(%)*	*Low group (n=220)*	*Medium group (n=149)*	*Full group (n=171)*	*Statistic*	*P-Value*
Oxygen metabolism (O)					χ^2=24.33	0.002*
uneven distribution	39(7.22)	19(8.64)	13(8.72)	7(4.09)		
Utilization of obstacles	17(3.15)	4(1.82)	3(2.01)	10(5.85)		
Insufficient oxygen supply	183(33.89)	72(32.73)	43(28.86)	68(39.77)		
Excessive oxygen consumption	223(41.30)	81(36.82)	75(50.34)	67(39.18)		
Normal	78(14.44)	44(20.00)	15(10.07)	19(11.11)		
Perfusion (P)					-	0.014*
unclear	1(0.19)	0(0.00)	0(0.00)	1(0.58)		
Low perfusion	341(63.15)	139(63.18)	98(65.77)	104(60.82)		
Low perfusion-anterior insufficiency type	41(7.59)	7(3.18)	13(8.72)	21(12.28)		
Low perfusion-stasis type	22(4.07)	6(2.73)	8(5.37)	8(4.68)		

Variable	*All N(%)*	*Low group (n=220)*	*Medium group (n=149)*	*Full group (n=171)*	*Statistic*	*P-Value*
Heterogeneous hypoperfusion	13(2.41)	5(2.27)	5(3.36)	3(1.75)		
Normal	122(22.59)	63(28.64)	25(16.78)	34(19.88)		
Arterial tension (A)					-	0.029*
Uncertain	3(0.56)	1(0.45)	0(0.00)	2(1.17)		
Low	397(73.52)	157(71.36)	114(76.51)	126(73.68)		
High	50(9.26)	13(5.91)	16(10.74)	21(12.28)		
Normal	90(16.67)	49(22.27)	19(12.75)	22(12.87)		
Cardiac Output (CO)					-	0.009*
unclear	1(0.19)	0(0.00)	0(0.00)	1(0.58)		
Due to pulmonary arterial hypertension	12(2.22)	5(2.27)	4(2.68)	3(1.75)		
Normal	114(21.11)	61(27.73)	22(14.77)	31(18.13)		
Due to left heart failure	355(65.74)	142(64.55)	104(69.80)	109(63.74)		
Due to hyperdynamic left heart	40(7.41)	7(3.18)	12(8.05)	21(12.28)		
Due to left heart end-diastolic volume preload insufficiency	18(3.33)	5(2.27)	7(4.70)	6(3.51)		
Systemic Congestion (C)					-	0.683
Grade 0	409(75.74)	163(74.09)	114(76.51)	132(77.19)		
Grade I	99(18.33)	46(20.91)	27(18.12)	26(15.20)		
Grade II	22(4.07)	9(4.09)	5(3.36)	8(4.68)		
Grade III	9(1.67)	2(0.91)	3(2.01)	4(2.34)		
Uncertain	1(0.19)	0(0.00)	0(0.00)	1(0.58)		
Unregulated Host response (U)					-	0.853
Dysregulation of the non-septic inflammatory response	81(15.00)	36(16.36)	22(14.77)	23(13.45)		
hyperoxia	26(4.81)	7(3.18)	7(4.70)	12(7.02)		
Dysregulation of the blood clotting reaction	13(2.41)	4(1.82)	5(3.36)	4(2.34)		
Dysregulation of the inflammatory response in sepsis	363(67.22)	151(68.64)	100(67.11)	112(65.50)		
Oxygen distribution anomaly	10(1.85)	5(2.27)	2(1.34)	3(1.75)		
Oxygen utilization disorders	10(1.85)	2(0.91)	4(2.68)	4(2.34)		
CNS + autonomic response	37(6.85)	15(6.82)	9(6.04)	13(7.60)		
Lesion Search (S)					χ^2=0.95	0.917
Bleeding located	28(5.19)	10(4.55)	8(5.37)	10(5.85)		
Infection located	413(76.48)	166(75.45)	115(77.18)	132(77.19)		
Injured located	99(18.33)	44(20.00)	26(17.45)	29(16.96)		

Note: * Represents P < 0.05.

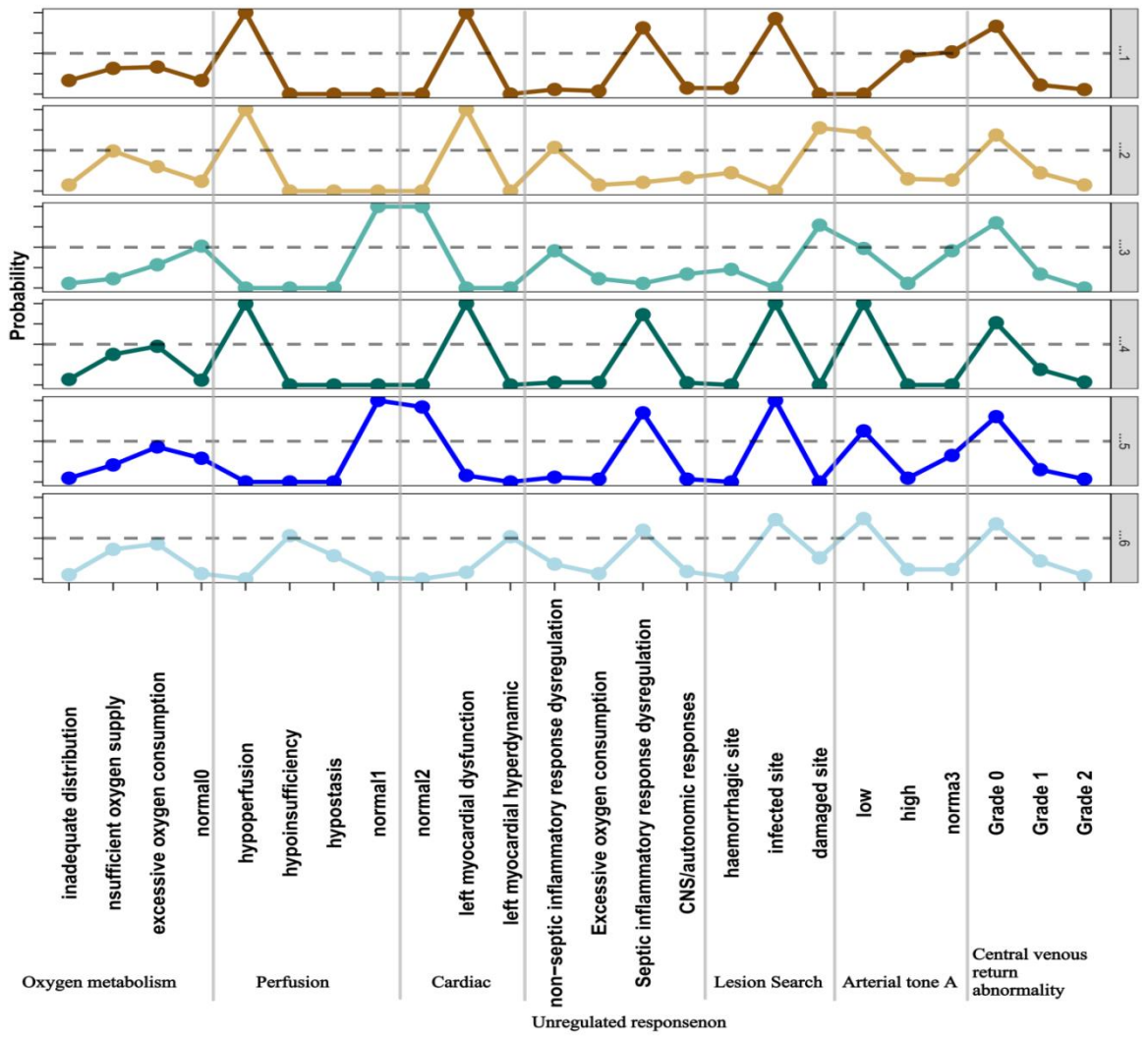


Figure 2-5: LCA Clustering model fit

Table 2-9: Distribution of shock phenotypes in LCA subgroups

Variable	All N (%)	Low group (n=220)	Medium group (n=149)	Full group (n=171)	Statistic	P-value
LCA subgroup					χ^2=19.42	0.035*
Group 1	54(10.00)	20(37.04)	17(31.48)	17(31.48)		
Group 2	67(12.41)	26(38.81)	17(25.37)	24(35.82)		
Group 3	35(6.48)	21(60.00)	8(22.86)	6(17.14)		
Group 4	221(40.93)	93(42.08)	65(29.41)	63(28.51)		
Group 5	86(15.93)	41(47.67)	17(19.77)	28(32.56)		
Group 6	77(14.26)	19(24.68)	25(32.47)	33(42.86)		

Note: * Represents P value ≤0.05.

Table 2-10: Comparison of LCA Subgroups and Patient Outcomes

Variable	***ALL N(%)***	**Group1 (n=54)**	**Group2 (n=67)**	**Group3 (n=35)**	**Group4 (n=221)**	**Group5 (n=86)**	**Group6 (n=77)**	**Statistic *P-value***
Outcome, n(%)								χ^2=22.67<0.001*
Survival	380(70.37)	40(74.07)	54(80.60)	31(88.57)	133(60.18)	67(77.91)	55(71.43)	
Non-survival	160(29.63)	14(25.93)	13(19.40)	4(11.43)	88(39.82)	19(22.09)	22(28.57)	

2.9 Validation of OPACCUS Protocol Execution Grouping

To validate the stability of prognostic outcomes across different quantiles in the OPACCUS grouping, we excluded individuals with a full execution rate. The remaining individuals, with OPACCUS execution rates below 1, were grouped in 5-point intervals from Q5 to Q95. The KM curves for the three groups showed nearly identical trends, suggesting that our grouping results maintain a degree of stability across various conditions. See Figure 2-6 and Figure 2-7 for further details.

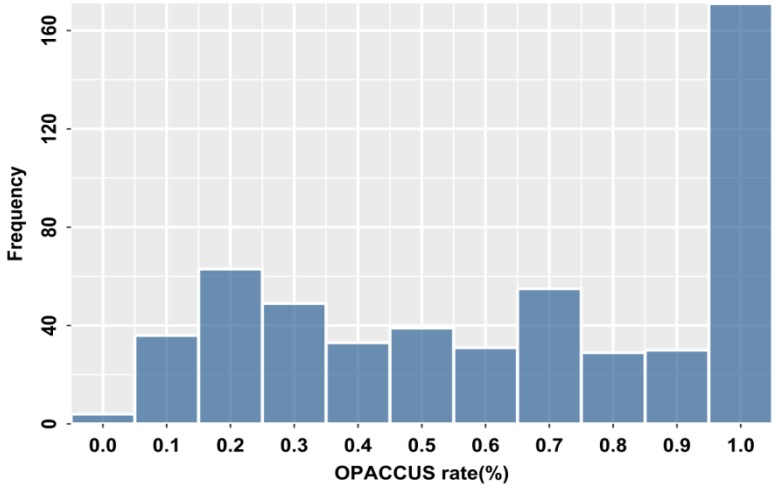


Figure 2-6: Histogram of the Frequency Distribution of OPACCUS Execution Rates (%)

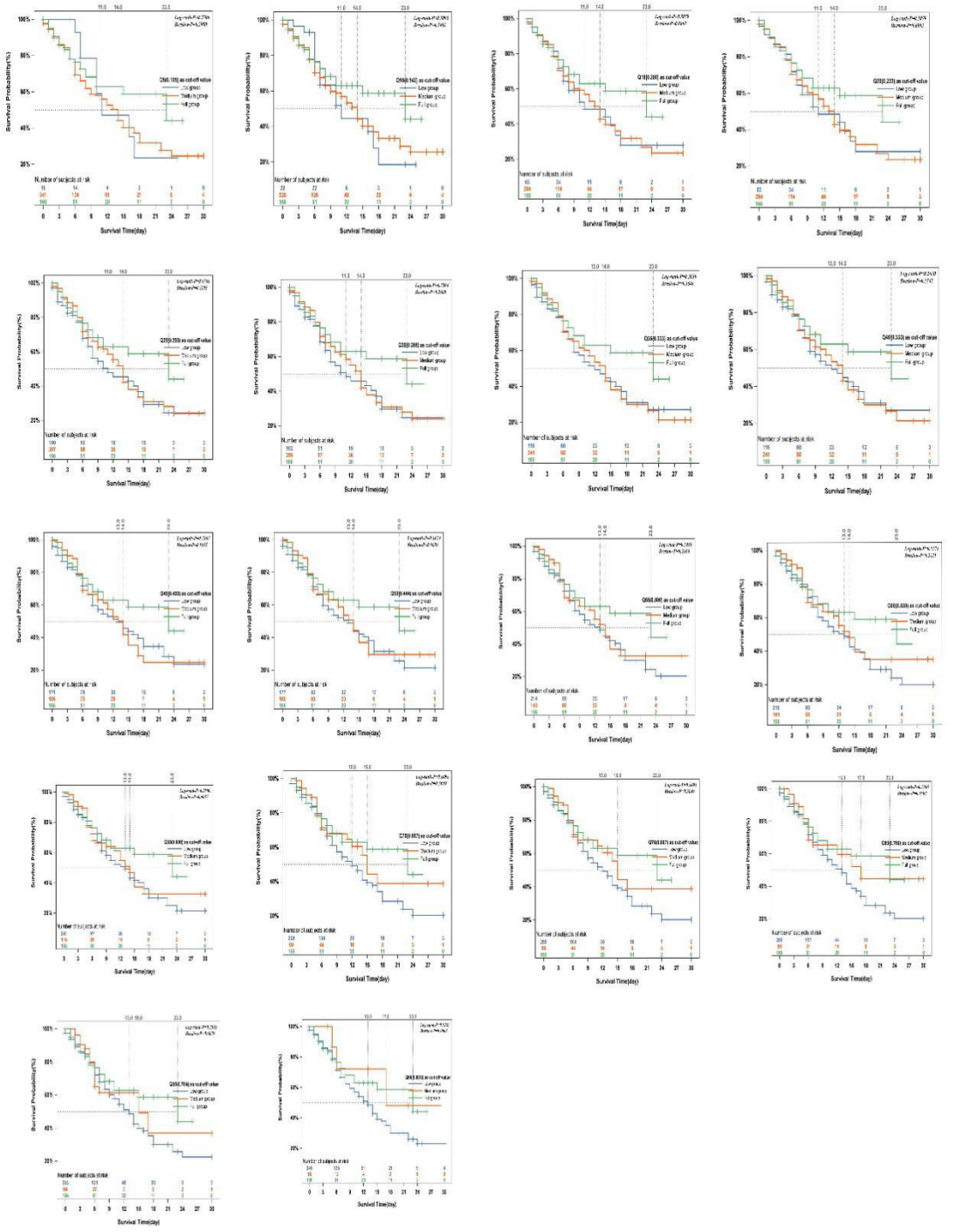


Figure 2-7: Kaplan-Meier Curve Analysis Results for Q5~Q95 at Different Quantiles.

Discussion

Shock is a critical and acute pathological state characterized by systemic hemodynamic instability that results in inadequate tissue perfusion. This inadequate perfusion leads to cellular hypoxia, metabolic dysfunction, and, ultimately, multiple organ dysfunction syndrome. If not promptly and effectively managed, shock can progress rapidly to a life-threatening situation, often with a high mortality rate[65]. The prevalence and severity of shock in hospital settings underscore the urgency for efficient and effective management strategies, making it a central concern in acute and critical care medicine.

Early diagnosis and timely intervention are crucial in managing shock effectively, as the condition is more likely to be reversible in its early stages. During these initial phases, the pathophysiological changes may still be amenable to intervention, allowing for restoration of perfusion and reversal of organ dysfunction. However, any delay in recognizing the condition or initiating appropriate treatment can lead to a rapid decline, pushing the patient toward irreversible organ damage and significantly increasing the risk of mortality[33].

In general wards, where the environment and resources are often less ideal for the management of acute conditions, the challenge of managing shock is even more pronounced. Limited medical resources and the potential lack of specialized expertise among healthcare providers in general wards can impede the prompt recognition and effective management of shock. Additionally, the lack of standardized guidelines specifically tailored to the management of shock in non-ICU settings can result in inconsistent practices and delays in delivering critical care. Shock management often necessitates advanced medical interventions, such as high-flow oxygen therapy, mechanical ventilation, the administration of vasoactive agents, continuous cardiac monitoring, and the use of sophisticated hemodynamic monitoring devices like PICCO systems[66, 67]. These interventions require specialized equipment and expertise typically not available in general wards, thereby complicating the management of shock in these settings.

Given these limitations, when shock is identified in a general ward, it becomes imperative to transfer the patient to an intensive care unit without delay. ICUs are

equipped to provide comprehensive and specialized care, including more advanced monitoring and therapeutic options, which are critical for managing the complex and rapidly evolving condition of shock. Early transfer to an ICU setting allows for the initiation of aggressive resuscitation strategies, continuous hemodynamic monitoring, and the implementation of targeted therapies that are essential for optimizing patient outcomes and improving survival rates[68]. Despite the clear need for rapid ICU transfer, there is a significant gap in research concerning the impact of delays in transferring shock patients from general wards to the ICU. Specifically, there is a lack of systematic studies that evaluate how these delays affect clinical outcomes and overall prognosis.

To address this gap, the current study aims to systematically evaluate the impact of ICU transfer timing on the prognosis of shock patients initially managed in general wards. Specifically, the study explores the value of early ultrasound-assisted diagnosis and treatment in improving shock patient outcomes, while identifying core clinical and ultrasound-based indicators related to prognosis. Additionally, the research investigates the relationship between suboptimal treatment practices in general wards and patient outcomes, providing a foundation for the development and validation of a new ultrasound-based shock management protocol. Moreover, this study aims to develop and validate the OPACCUS protocol, a new shock evaluation and treatment framework based on visualized ultrasound information. By integrating critical care ultrasound and clinical data, the OPACCUS protocol focuses on etiology management, precise hemodynamic treatment, and systemic response interventions to improve patient outcomes. A multicenter study will further evaluate the clinical application of the OPACCUS protocol, assessing its effects on key outcomes such as mortality, hospital stay duration, and healthcare costs. The study will also test the protocol's feasibility and effectiveness in diverse clinical settings. Ultimately, this research seeks to standardize and optimize shock management protocols. Through the implementation and refinement of the OPACCUS protocol, it aims to provide specific clinical practice recommendations that enhance the precision and efficiency of shock patient management.

1. Evaluation of ICU Transfer Timing and Ultrasound-Guided Diagnosis and Treatment for the Prognosis of Shock Patients: Core Indicator Selection and Early Strategy Enhancement

1.1 General Discussion of Shock

This study focused on patients experiencing shock who were transferred from general wards to the intensive care unit between January 31, 2019, and January 31, 2024. A total of 3,535 patients were included, with a mean age of 56.4 ± 15.3 years. Among these patients, 2,317 (65.5%) were male, and 1,218 (34.5%) were female. The majority of the patients were of Han Chinese ethnicity, comprising 1,981 individuals (56.0%). The average length of hospitalization was 21.5 ± 21.7 days, while the mean ICU stay was 7.77 ± 13 days (interquartile range: 2.30-8.74 days). The overall in-hospital mortality rate was 24.0%, with 850 patients succumbing during their stay. The mean duration of shock time was 39.6 ± 29.3 hours, and at the onset of shock, the median SOFA score was 11 (interquartile range: 9-12), and the APACHE II score was 26 (interquartile range: 22-29). Within 24 hours of ICU admission, the median SOFA score remained at 11 (interquartile range: 10-13), and the APACHE II score was 26 (interquartile range: 22-29).

The types of shock observed in this cohort were primarily distributive shock, affecting 2,392 patients (67.7%), followed by hypovolemic shock in 1,099 patients (31.1%), cardiogenic shock in 123 patients (3.48%), and obstructive shock in 98 patients (2.77%). Among the cases of distributive shock, septic shock was the most prevalent, accounting for 2,282 patients (64.6%). Hemorrhagic shock, a subset of hypovolemic shock, was observed in 529 patients (15.0%). Throughout the study period, there was a notable increase in the incidence of distributive shock, accompanied by a rising trend in in-hospital mortality across all shock types. The mean duration of shock time also varied by type, with distributive shock lasting an average of 42.21 ± 29.89 hours, hypovolemic shock 36.55 ± 27.04 hours, cardiogenic shock 39.8 ± 33.32 hours, and obstructive shock 29.47 ± 26.94 hours.

The patient cohort presented a diverse range of diagnoses. The most common condition was severe pneumonia, affecting 1,882 patients (53.2%), followed by acute respiratory failure in 650 patients (18.4%), acute circulatory disorders in 375 patients

(10.6%), acute pancreatitis in 818 patients (23.1%), renal failure in 614 patients (17.4%), hepatic failure in 996 patients (28.2%), central nervous system disorders in 278 patients (7.86%), and diabetes in 586 patients (16.6%). Additionally, 89 patients (2.52%) experienced cardiac arrest during their admission and received cardiopulmonary resuscitation.

Despite the critical nature of the shock, there remains limited research on the prognostic impact of delays in transferring shock patients from general wards to the ICU. The clinical trajectory of shock patients is often unpredictable, complicating efforts to anticipate deterioration and intervene early. Understanding the consequences of delayed transfers is crucial, as it can help identify patients at higher risk and facilitate more timely and effective interventions. Studies have consistently demonstrated that patients requiring unplanned ICU transfers often experience rapid disease progression, leading to poorer outcomes, including higher mortality rates and prolonged hospital stays[69, 70]. For instance, Odetola et al. found that the mortality rate for patients transferred to the Pediatric Intensive Care Unit (PICU) from general pediatric wards was 9.8%, compared to 3.7% for those transferred from the pediatric emergency department and 2.2% for those transferred after elective surgery[71]. In contrast, our study revealed that the mortality rate for patients with unplanned transfers from general wards to the ICU due to shock was a concerning 24%. Furthermore, the 90-day mortality rate for septic shock patients transferred from the emergency department to the ICU was reported at 18.67% in a separate study[72], a figure close to our findings.

Septic shock, a type of distributive shock, was the most prevalent form of shock in our study, followed by hypovolemic and cardiogenic shock, with obstructive shock being relatively rare. These findings align with previous research, such as a study involving over 1,600 shock patients, where septic shock accounted for 62% of cases, cardiogenic shock for 16%, hypovolemic shock for 16%, and obstructive shock for 2%[73]. In our cohort, distributive shock affected 67.7% of patients, hypovolemic shock 31.1%, cardiogenic shock 3.48%, and obstructive shock 2.77%. Among those with distributive shock, septic shock constituted 64.6% of cases, while hemorrhagic shock represented 15.0% of hypovolemic shock cases. These data underscore the significant

burden of septic shock in hospital settings.

Accurate identification of the type and cause of shock is critical for effective management and often relies on a combination of patient history, physical examination, and clinical testing. For example, post-traumatic shock is typically hypovolemic due to blood loss, but cardiogenic or distributive shock may also occur, either alone or in combination. Early utilization of focused echocardiography in patients presenting with shock symptoms is essential for determining the underlying cause, enabling timely and appropriate management strategies[74-76].

1.2 Baseline Comparison of Subgroups of Delayed Transfers from General Wards to ICUs for Patients Experiencing Shock

Timely intervention in managing shock, particularly septic shock, has been established as a critical factor in improving patient outcomes over the past two decades. A pivotal randomized prospective clinical trial in 2001 highlighted that early goal-directed therapy (EGDT), administered within the first six hours of patient presentation in the emergency room, significantly reduced in-hospital mortality among sepsis patients—from 46.5% to 30.5%[77]. Following this, numerous medical centers worldwide adopted EGDT protocols, which demonstrated substantial reductions in mortality compared to historical controls or patients who did not receive EGDT[78, 79]. The success of EGDT in enhancing patient survival led to its swift integration into sepsis management guidelines by 2004, where it became the standard of care[80].

Subsequent studies have continued to emphasize the importance of early intervention in shock management. A comprehensive analysis of data from the New York State Department of Health between 2014 and 2016 revealed that delays in completing sepsis-related interventions within the first three hours were associated with higher in-hospital mortality rates among patients with sepsis and septic shock[81]. Among the delays, those in administering antibiotics were found to have a more pronounced impact on mortality than delays in fluid resuscitation[82]. Reflecting evolving perspectives in clinical management, the 2021 Guidelines for Safe Laboratories revised previous recommendations, now permitting greater flexibility in administering fluids and antibiotics in cases where shock and sepsis are not definitively diagnosed[83].

Recognizing the critical nature of early intervention, our study categorized transfer times from general wards to ICUs following the onset of shock into three distinct groups: Group 1 (pre-ICU shock time <3 hours), Group 2 (pre-ICU shock time: 3-6 hours), and Group 3 (pre-ICU shock time >6 hours). These categories were chosen based on identified critical time windows for early intervention, particularly emphasizing the first six hours, with the first three hours being crucial for optimizing shock management outcomes.

This retrospective cohort study aimed to investigate the relationship between varying transfer delay times and mortality outcomes in patients experiencing shock who were transferred from general wards to ICUs. The analysis involved a comprehensive comparison of baseline characteristics across different delay time groups, followed by an assessment of the association between transfer delay time and in-hospital mortality using various analytical methods, including Kaplan-Meier survival curves, logistic regression analyses, Area Under the Curve analyses, and restricted cubic spline regression models.

By employing these multifaceted analytical approaches, our study provides a deeper understanding of how the timing of ICU transfers affects patient outcomes. The results are anticipated to offer valuable insights into optimizing the timing of interventions, ultimately contributing to improved clinical practices and enhanced survival rates for patients in shock.

Through a detailed analysis of our study, we observed that when patients in the general ward experienced shock and were transferred to the ICU within 3 hours, the distribution of shock types revealed that the highest percentage of patients were those with distributive shock, comprising 66.1% of the cohort. Hypovolemic shock patients accounted for 32.2%, and cardiogenic shock patients represented 3.16%. This distribution highlights a critical observation: patients with distributive and hypovolemic shock are typically identified and transferred to the ICU for advanced care more rapidly during the early stages of their condition. The predominance of distributive shock, which accounts for nearly two-thirds of all shock pathologies, aligns with existing literature that underscores its frequency in clinical settings[73, 84].

Our study also provided insights into the primary diagnoses associated with shock

in these patients. Severe pneumonia was the most prevalent condition, affecting 48.4% of the patient cohort, followed by hepatic failure (25.4%), acute pancreatitis (21.6%), renal failure (14.5%), diabetes mellitus (15.9%), acute respiratory failure (12.1%), circulatory disorders (7.90%), and central nervous system disorders (7.86%). Notably, severe pneumonia and acute pancreatitis were frequently associated with the development of septic and hypovolemic shock, respectively—both of which significantly contribute to hospital admissions and mortality in critically ill patients[85-87]. For instance, severe pneumonia in the United States alone leads to approximately 423,000 emergency room visits annually, with a mortality rate of 15.9 deaths per 100,000 people[88].

Additionally, our findings indicated that in the first group (patients transferred within 3 hours), the incidence of these primary diagnoses was relatively lower compared to other groups. This suggests that early identification and intervention may have mitigated the progression of their conditions, thereby reducing the severity of their shock and improving overall outcomes.

Significantly, the proportion of patients requiring cardiopulmonary resuscitation (CPR) was much lower in this early transfer group, with only 6.00% of patients receiving CPR, compared to higher rates in groups with longer transfer times. The reduced need for such critical interventions underscores the benefits of prompt ICU admission, allowing for early and aggressive treatment that can prevent the escalation of shock and improve patient prognosis. This observation aligns with the broader consensus that early intervention is crucial in managing shock, as it significantly reduces the risk of deterioration and mortality in critically ill patients[89, 90]. Early intervention not only enhances survival rates but also reduces the likelihood of severe complications, highlighting the importance of rapid ICU transfer for patients experiencing shock.

We conducted a comprehensive statistical analysis of the baseline vital signs and laboratory indices across the three groups of patients, evaluating the statistical differences to understand the impact of delayed transfer to the ICU after the onset of shock in the general ward. Our findings revealed significant variations in clinical parameters between the groups, particularly within the first 24 hours after ICU

admission.

In the third group (patients transferred more than 6 hours after the onset of shock), the median APACHE II score was 28.0 [25.0; 31.0], and the median SOFA score was 12.0 [11.0; 14.0]. These scores were significantly higher than those in the other groups, indicating greater severity of illness in these patients. Additionally, this group exhibited a respiratory rate of 22.8 ± 5.17 breaths/min, a temperature of 37.8 ± 1.03°C, a heart rate of 120 ± 27.6 beats/min, a C-reactive protein level of 127 ± 109 mg/L, an International Normalized Ratio of 1.59 ± 0.84, a troponin T level of 181 ± 549 ng/mL, a lactate level of 4.76 ± 4.71 mmol/L, sodium levels at 145±5.87 mmol/L, creatinine levels at 149±5.87 μmol/L, blood urea nitrogen levels at 11.9±8.68 mg/dL, and blood glucose levels at 10.8±3.81 mmol/L. These elevated indices underscore the critical condition of patients in the third group, who exhibited significantly worse physiological and laboratory indicators than those in the other groups.

In contrast, within 24 hours after ICU admission, patients in the first group (transferred within 3 hours of shock onset) demonstrated relatively more stable vital signs and laboratory indicators. Their blood pressure levels (diastolic blood pressure: 52.5 ± 7.92 mmHg, systolic blood pressure: 96.5 ± 15.4 mmHg, and mean arterial blood pressure: 67.9 ± 9.65 mmHg), oxygen saturation 97.8 ± 4.64%, PaO2: 94.2±33.3 mmHg, PaO2/FiO2 ratio (223±91 mmHg), erythrocyte count (3.47±0.72 × 10^12/L), albumin levels (34.2±6.44 g/L), hemoglobin levels (104±20.5 g/L), and platelet levels (159±105 × 10^9/L) were all higher compared to the other groups. This suggests that these patients were less critically ill upon ICU admission, with more stable physiological parameters and a less severe disease state.

The APACHE II and SOFA scores, well-established tools for assessing the severity and prognosis of critically ill patients, played a crucial role in our analysis. The APACHE II score considers multiple risk factors, including major signs and physiological indicators, while the SOFA score evaluates the function of six organ systems: circulatory, respiratory, coagulation, hepatic, renal, and neurological systems[91, 92]. The APACHE II score involves several risk factors, including major signs and physiologic indicators[93, 94]. The APACHE II score involves a number of risk factors, including the main signs and physiological parameters of the patient , while

the SOFA score covers six organ systems: circulatory, respiratory, coagulation, hepatic, renal, and neurological[95]. Our findings demonstrated that group 1 had the lowest APACHE II and SOFA scores, indicating a lower severity of illness, whereas group 3 had the highest scores, reflecting a more critical condition.

This disparity in scores between groups underscores the importance of timely ICU transfer. Patients transferred rapidly (within 3 hours) were less severely ill, suggesting that early ICU admission allows for more effective intervention before significant deterioration. In contrast, delayed transfer was associated with greater severity of illness, as indicated by higher APACHE II and SOFA scores, alongside more unstable vital signs and laboratory indicators.

These findings strongly emphasize the critical importance of early ICU transfer for patients experiencing shock. Prompt ICU admission facilitates timely and aggressive treatment, potentially preventing the progression of shock and improving overall outcomes. The data emphasize the importance of healthcare teams prioritizing rapid intervention and transfer for shock patients, as delays can lead to significantly worse prognoses and increased mortality risks.

1.3 Discussion of Lactate Levels and Blood Creatinine, Platelet and TnT Levels

Lactate levels are a crucial clinical marker used to assess circulatory perfusion in shock patients, serving as a vital indicator of tissue hypoperfusion and metabolic distress[96-98]. Elevated lactate levels often signify inadequate oxygen delivery to tissues, leading to anaerobic metabolism and subsequent lactate accumulation. Numerous studies have validated the close relationship between lactate levels and tissue perfusion status. Improvements in perfusion are typically associated with reduced lactate concentrations, indicating effective therapeutic intervention and a better prognosis[99, 100]. Conversely, persistently elevated lactate levels correlate with worsening perfusion and are often indicative of a poor response to treatment and a graver overall prognosis. The concept of using lactate levels as a therapeutic response indicator has been well-established since 1983, with consistent findings that a reduction in blood lactate levels is associated with improved outcomes in critically ill patients[101-104]. Consequently, lactate monitoring has become a standard practice in managing patients with shock, providing real-time insights into the effectiveness of

therapeutic interventions.

In our study, lactate levels were meticulously tracked to evaluate the impact of different transfer times on the outcomes of shock patients. The findings revealed a clear pattern: patients in the first group (transferred to the ICU within 3 hours of shock onset) exhibited significantly lower lactate levels compared to those in the second and third groups. Specifically, in the first group, lactate levels showed a notable decline: 3.63±3.12 mmol/L at 6 hours, 2.78±2.44 mmol/L at 24 hours, 2.05±1.67 mmol/L at 48 hours, and 1.93±1.62 mmol/L at 72 hours. This consistent and rapid decline in lactate levels underscores the importance of timely ICU transfer and early intervention, which appear to markedly improve tissue perfusion and, consequently, patient outcomes.

In contrast, patients in the second and third groups, who experienced delays in ICU transfer, maintained higher lactate levels across all time points, with a less pronounced overall decline. For instance, the third group (transferred more than 6 hours after shock onset) had lactate levels of 4.72 ± 4.29 mmol/L at 6 hours, 3.31 ± 3.29 mmol/L at 24 hours, 2.83 ± 2.75 mmol/L at 48 hours, and 2.42 ± 1.98 mmol/L at 72 hours. This slower reduction in lactate levels suggests that delayed transfer impedes the effectiveness of early therapeutic measures, leading to prolonged periods of poor perfusion and a potentially higher risk of adverse outcomes. These findings align with previous research that underscores the prognostic value of lactate clearance in critically ill patients[105, 106].

In addition to lactate levels, our study also examined other critical biomarkers, including blood creatinine, platelet count, and troponin T (TnT) levels, which are integral to assessing renal function, coagulation status, and myocardial injury, respectively. These biomarkers provide a comprehensive overview of organ function and the physiological state of patients experiencing shock.

Creatinine is a byproduct of muscle metabolism, and its levels in the blood reflect kidney function[107, 108]. In shock patients, elevated creatinine levels could indicate impaired renal perfusion and acute kidney injury (AKI), a common complication of shock. In our study, blood creatinine levels were significantly lower in the first group across all measured time points (24, 48, and 72 hours), suggesting better renal perfusion and function. For example, at 24 hours, the creatinine levels in the first group

were 95.2 ± 86.6 μmol/L, compared to 146 ± 136 μmol/L in the third group. This suggests that early intervention and timely ICU transfer may help maintain renal function, likely due to more effective fluid resuscitation and hemodynamic stabilization achieved through prompt care[109, 110].

Platelets play a critical role in coagulation and maintaining hemostasis. A decrease in platelet count (thrombocytopenia) is common in critically ill patients and can result from various factors, including sepsis, disseminated intravascular coagulation (DIC), and direct platelet consumption. In our study, although a general decline in platelet levels was observed in all groups, the decline was less severe in the first group, suggesting a potentially reduced risk of coagulation disorders and related complications in patients who received early intervention. For instance, at 48 hours, the platelet count in the first group was 120±88.5 × 10^9/L, whereas it dropped to 101±74.9 × 10^9/L in the third group. This difference underscores the benefit of early ICU transfer in minimizing the progression of coagulopathy and maintaining better hemostatic control[111, 112].

Troponin T is a specific marker of myocardial injury, and elevated levels indicate cardiac muscle damage, which is often seen in shock patients due to reduced coronary perfusion and increased myocardial oxygen demand[113, 114]. Our study found that TnT levels were consistently lower in the first group than in the second and third groups. For example, at 24 hours, TnT levels in the first group were 65.5±299 ng/mL compared to 172±516 ng/mL in the third group. This suggests that early ICU transfer may mitigate the cardiac strain often seen in shock patients, possibly due to earlier hemodynamic stabilization and more effective management of myocardial oxygen supply-demand balance.

These findings collectively reinforce the critical importance of prompt ICU transfer and early intervention in the management of shock. Early and aggressive treatment, facilitated by timely transfer, appears to significantly improve key clinical indicators, thereby stabilizing the patient's condition and enhancing the overall prognosis. The marked differences in lactate, creatinine, platelet, and TnT levels between the groups highlight the detrimental impact of delayed transfer, further underscoring the necessity for rapid decision-making and action in the care of shock

patients. Rapid identification and response to shock, particularly in the early stages, are paramount to preventing multi-organ failure and reducing mortality rates in critically ill patients.

1.4 Comparative discussion of duration of mechanical ventilation, ultrasound, use of antibiotics, vasoactive drug use, duration of working holiday, duration of hospitalization, and duration of ICU stay

Mechanical Ventilation Duration

Our study demonstrated a significant difference in the duration of mechanical ventilation across the three groups. The shortest duration was observed in the first group (98.0 ± 165 hours), followed by the second group (214 ± 440 hours) and the third group (240 ± 280 hours) ($P<0.001$). The reduced mechanical ventilation time for patients transferred to the ICU within 3 hours of shock onset suggests that early ICU admission is associated with a decreased need for prolonged mechanical ventilation. This finding implies that early intervention in the ICU helps mitigate respiratory compromise more effectively, potentially reducing complications associated with extended mechanical ventilation, such as ventilator-associated pneumonia, muscle weakness, and increased ICU length of stay.

Ultrasound Utilization

Ultrasound utilization within 6 hours of shock onset was significantly higher in the first group ($P<0.001$). This finding indicates that early transfer to the ICU facilitates more timely and frequent use of ultrasound for patient evaluation. Early ultrasonography is crucial for the rapid assessment and adjustment of treatment strategies, optimizing patient management, and improving prognosis[48, 115]. In acute critical care, ultrasound serves as a non-invasive tool vital for diagnosing and managing patients[49]. It enables rapid differentiation of shock types and aids in the early diagnosis and intervention in general wards, facilitating timely transfer to the ICU for further intensive care. Prior studies have demonstrated that ultrasound improves outcomes in critically ill patients[116], particularly by assisting in the diagnosis and differentiation of shock types, which guides further therapeutic interventions[48, 117]. Ultrasound is especially important for evaluating circulatory disorders and assessing fluid resuscitation, making it an essential tool for managing

patients with shock[47, 50].

However, no significant difference in ultrasound utilization was observed within the ICU over a 24-hour period (P=0.94). This suggests that, once in the ICU, the frequency and standards of ultrasound use remain consistent regardless of transfer time. This uniformity underscores the importance of early intervention and reinforces the value of establishing consistent practices for ultrasound use in critical care settings to ensure optimal patient outcomes.

Antibiotic Use

Antibiotic utilization was notably higher in the first group, with 31.6% of patients receiving antibiotics within 6 hours of shock onset, compared to 22.7% in the second group and 10.1% in the third group (P<0.001). This increased early antibiotic use in the first group reflects the advantage of early ICU transfer in initiating timely antibiotic therapy, which is crucial for managing septic shock and improving outcomes[118, 119]. Early administration of antibiotics is vital for reducing the bacterial load and preventing the progression of infection to severe sepsis or septic shock, conditions associated with high mortality rates.

Vasoactive Drug Use

The first group had significantly lower norepinephrine use (32.1 ± 70.0 mg) compared to the second (69.1 ± 89.8 mg) and third groups (104 ± 154 mg) (P<0.001). This suggests that early transfer to the ICU may result in less reliance on vasoactive medications, potentially due to more effective hemodynamic stabilization achieved through early intervention. Lower use of norepinephrine in the first group may also indicate that early resuscitation efforts were more successful in achieving hemodynamic stability, reducing the need for aggressive vasopressor therapy. While the exact reasons for the variability in norepinephrine use require further investigation, this trend underscores the benefits of prompt ICU admission in optimizing cardiovascular support and minimizing the risks associated with high-dose vasopressor use, such as arrhythmias and tissue ischemia.

Timing of Shock Events and ICU Transfer

The proportion of shock events occurring during non-working hours was highest in the third group (47.0%) compared to the first group (44.0%) (P=0.075). Although

this difference was not statistically significant, it suggests that a higher proportion of severe cases may arise during off-hours, potentially affecting the timing of ICU transfers. The higher percentage of transfers during non-working hours in the first group (46.2%) might indicate the influence of temporal factors on resuscitation and transfer processes, potentially impacting the availability of staff and resources, and thus the speed and effectiveness of the response to shock.

Total Shock Duration Time and ICU Admission Time

The total shock duration and delay in transfer to ICU admission were significantly shorter in the first group (32.8 ± 23.4 hours) compared to the second group (39.2 ± 24.2 hours) and the third group (75.6 ± 32.4 hours) ($P<0.001$). This marked reduction in shock duration for the first group underscores the advantages of early ICU transfer. By minimizing the total time patients spend in shock, early transfer can reduce the risk of prolonged tissue hypoperfusion and subsequent organ damage, which are critical factors in patient prognosis. Faster ICU admission enables more timely and targeted interventions, such as optimized fluid resuscitation, vasopressor support, and advanced monitoring, which can stabilize patients more rapidly and improve overall outcomes. Thus, early ICU transfer plays a vital role in the management of shock, potentially reducing the incidence of multi-organ dysfunction and enhancing patient recovery.

Duration of Hospitalization and ICU Stay

Patients in the first group experienced significantly shorter total hospitalization (19.9 ± 17.9 days) and ICU stay (6.83 ± 10.2 days) compared to those in the second and third groups ($P<0.001$). These findings suggest that early ICU transfer not only reduces the length of ICU stay but also the overall hospitalization duration, reflecting a more efficient recovery process and better prognosis. Shorter ICU stays reduce the risk of complications related to prolonged ICU care, such as infections, delirium, and muscle atrophy, and lead to more efficient use of hospital resources. The decreased length of hospitalization also highlights the benefits of early and aggressive management strategies in shock patients, allowing for faster stabilization and recovery.

1.5 Prognostic analysis discussion

Our study's prognostic analysis revealed significant differences in in-hospital mortality rates among the three groups of patients, emphasizing the critical role of

timely ICU transfer in shock management. The first group, with the shortest pre-ICU shock time, exhibited the lowest mortality rate at 18.0% (513 patients). In contrast, the second group had a markedly higher mortality rate of 40.7% (61 patients), and the third group experienced the highest mortality rate at 51.5% (276 patients). The significantly lower in-hospital mortality rate in Group 1 compared to Groups 2 and 3 underscores the importance of early ICU transfer in reducing mortality. Conversely, the substantially higher mortality rate in Group 3 highlights the detrimental impact of delayed ICU admission on patient outcomes.

Kaplan-Meier survival curves further illustrated the stark contrast in outcomes among the groups. Patients in Groups 2 and 3 had significantly lower survival rates at both 28 and 60 days compared to those in Group 1 (log-rank $P<0.001$). Additionally, when patients were categorized into two groups based on pre-ICU shock time ($\leq$6 hours and >6 hours), similar trends were observed. Patients with pre-ICU shock times greater than 6 hours exhibited markedly lower survival rates at 28 and 60 days compared to those with shorter shock times (log-rank $P<0.001$). These findings suggest that extended pre-ICU shock times are associated with reduced long-term survival, reinforcing the critical need for prompt ICU admission to improve patient outcomes.

To explore the independent effect of pre-ICU shock time on mortality, we employed logistic regression models, analyzing pre-ICU shock time both as a continuous and categorical variable. In the univariate logistic regression analysis, pre-ICU shock time as a continuous variable emerged as a significant risk factor for in-hospital mortality (OR>1, $P<0.001$). Further analysis using multivariate logistic regression, adjusted for potential confounders in models 1, 2, and 3, consistently demonstrated that pre-ICU shock time remained a significant independent predictor of in-hospital mortality. Specifically, the odds ratio (OR) for continuous pre-ICU shock time in the fully adjusted model 3 was 1.023 (95% CI: 1.02-1.03, $P<0.001$), indicating a strong association between prolonged pre-ICU shock time and increased mortality risk.

Similar results were observed in the analysis of 28-day mortality. In the fully adjusted multivariate logistic regression model, the OR for 28-day mortality related to

pre-ICU shock time as a continuous variable was 1.01 (95% CI: 1.01-1.03), further reinforcing the significance of early ICU intervention in reducing mortality risk.

When pre-ICU shock time was analyzed as a categorical variable, a clear upward trend in in-hospital mortality was observed with increasing pre-ICU shock times. Using Group 1 (≤6 hours) as the reference, the OR for mortality in Group 2 (6-12 hours) was 3.12 (95% CI: 2.21-4.37), and in Group 3 (>12 hours), it was 4.83 (95% CI: 3.98-5.87) in the univariate analysis. After adjusting for potential confounders, these associations remained significant, with ORs of 2.21 (95% CI: 1.48-3.26) for Group 2 and 2.74 (95% CI: 2.17-3.47) for Group 3. These results indicate that delayed ICU transfer is a potent predictor of increased mortality, with the risk escalating as the delay lengthens.

To further investigate the relationship between pre-ICU shock time and in-hospital mortality, we applied a restricted cubic spline (RCS) regression model. The analysis revealed a nonlinear relationship, indicating that while the overall risk of in-hospital death increases with longer pre-ICU shock times, the rate of this increase varies over time.

The efficacy of pre-ICU shock time as a predictor of mortality was also assessed using receiver operating characteristic (ROC) curves. The area under the curve (AUC) for predicting in-hospital mortality was 0.672 (95% CI: 0.645-0.698), while the AUC for predicting 28-day mortality was 0.674 (95% CI: 0.651-0.696). These results indicate that pre-ICU shock time is a moderately strong predictor of both in-hospital and 28-day mortality, highlighting its potential utility in clinical decision-making.

Our findings align with previous research that underscores the critical impact of timely ICU admission on patient outcomes. For instance, studies have demonstrated that delays in transferring patients from the emergency department (ED) to the ICU are associated with increased mortality and prolonged mechanical ventilation times[30, 31]. Another retrospective study (2010 to 2018) found that prolonged ED stay was an independent predictor of increased hospital mortality[32]. However, some studies, such as those by Hirschy et al. and large population-based analyses, have not confirmed this association, suggesting that the quality of care in the ED might mitigate the effects of transfer delays[33, 34].

In the context of specific shock types, retrospective observational studies have shown varying results. For example, a study on septic shock patients found that early ICU transfer (within 4 hours) was associated with higher 90-day mortality, but this association was not significant after adjusting for confounders[72]. Our study's results, which demonstrate a clear link between delayed ICU transfer and increased mortality, are consistent with those of Zhang et al., who found that longer ED stays were an independent predictor of higher hospital mortality[32].

In this study, we also analyzed the impact of early ultrasound use, specifically within 6 hours of shock onset, on the prognosis of shock patients. Among the patients, 251 received ultrasound-assisted diagnosis and treatment within this critical time window. Our results demonstrated that early ultrasound use was significantly associated with improved clinical outcomes. These included a shorter median ICU stay (4.23 [2.16; 8.72] days vs. 5.13 [2.90; 9.00] days), a reduction in shock duration (34.7 ± 26.2 hours vs. 39.9 ± 29.5 hours), earlier ICU transfer (2.73 ± 9.12 hours vs. 5.49 ± 13.7 hours), lower in-hospital mortality rates (16.7% vs. 24.6%), and a marked reduction in 28-day ICU mortality (13.9% vs. 22.0%). The Kaplan-Meier survival analysis further supported these findings, showing a significantly higher 28-day survival rate in the early ultrasound group compared to the non-ultrasound group (log-rank $P<0.05$). Moreover, logistic regression analysis confirmed that early ultrasound use was an independent protective factor for both in-hospital and 28-day mortality. These results underscore the importance of early ultrasound intervention in improving patient outcomes by facilitating timely diagnosis and appropriate therapeutic strategies. The study by Basmaji et al. demonstrated that the use of point-of-care ultrasound (POCUS) during the resuscitation of shock patients positively influenced physician management, reduced the need for certain diagnostic tests, improved lactate clearance, and potentially shortened the duration of vasopressor use, reduced the need for renal replacement therapy, and decreased 28-day mortality[120]. Another study also confirmed that cardiac ultrasound improved diagnostic certainty or altered management in most patients, with management adjustments more frequently observed in patients with obstructive or cardiogenic shock (n=15 [75%] and n=100 [58%], respectively)[121]. These findings align with our study, which further validates

the importance of ultrasound use in intensive care units, particularly in the differential diagnosis of shock patients, and highlights its role in improving treatment efficiency and patient outcomes.

Additionally, the in-hospital mortality prediction model for shock patients we developed indicates that the Apache II score, SOFA score, acute respiratory failure, pneumonia, kidney failure, INR, blood lactate levels, sodium concentration, anion gap, PaO_2, and pre-ICU transfer time are independent risk factors, while serum albumin levels, lymphocyte count, PaO_2/FiO_2 ratio, and ultrasound examination within 6 hours shock onset are protective factors. The model's ROC curve, Hosmer-Lemeshow test, calibration curve, and decision curve analysis all demonstrate good calibration and clinical utility.

The identification of these core clinical indicators is critical, as it forms the foundation for the development and implementation of the OPACCUS protocol. By systematically selecting these key indicators, we can initiate and refine a more efficient shock management pathway through the OPACCUS diagnostic and treatment process. This approach aims to standardize the early identification and intervention for shock patients, ultimately enhancing the overall treatment efficiency and improving patient outcomes.

1.6 Research Limitations:

While our study provides valuable insights into the systematic evaluation of the timing of ICU transfer for shock patients in general wards, the importance of early ultrasound-guided diagnosis and treatment, and the identification of core indicators for optimizing early shock management strategies, several limitations must be acknowledged.

First, our research encompassed all types of shock, including septic, cardiogenic, hypovolemic, and distributive shock, among others. The clinical characteristics and management strategies for these different types of shock can vary significantly, which may limit the generalizability of our findings. For instance, the interventions and therapeutic approaches that are effective for one type of shock may not be equally effective for another. As a result, the broad inclusion of various shock types could have introduced heterogeneity into our analysis, potentially diluting the impact of specific

management strategies on patient outcomes.

Second, the practices surrounding the timing of patient transfers from general wards to the ICU can differ between hospitals. Factors such as hospital protocols, available resources, staffing levels, and even geographical location can influence how quickly a patient is moved to the ICU. These variations in practice may limit the applicability of our findings across different healthcare settings. Hospitals with faster transfer processes may see different outcomes than those with longer delays, which could affect the overall conclusions of the study.

Additionally, our study relied on retrospective data, which inherently carries the risk of bias. Retrospective studies, while useful for analyzing large datasets and generating hypotheses, are subject to limitations such as incomplete data, misclassification, and selection bias. These factors can impact the accuracy and reliability of the results. Although we employed rigorous statistical methods to control for potential confounders, the possibility of residual bias remains.

To address these limitations and enhance the robustness of our findings, future research should focus on conducting prospective randomized controlled trials (RCTs). RCTs would allow for a more controlled environment, reducing the impact of confounding variables and providing a higher level of evidence. Such trials could help clarify the specific effects of transfer timing on different types of shock and provide more definitive guidance for clinical practice.

1.7 Research Significance and Innovation

1.7.1 Significance of the Study

Shock is a critical condition characterized by severe hemodynamic instability and multi-organ dysfunction, often leading to life-threatening complications. The timely diagnosis and intervention in shock cases are essential for improving patient outcomes. However, the initial reversible nature of shock and its rapid progression make swift transfer to the ICU a crucial factor in patient survival. Despite this, there has been a relative scarcity of studies focusing on how delays in transferring shock patients from the general ward to the ICU affect their prognosis.

This study addresses this research gap through a systematic evaluation that incorporates the "four plus one" objectives, aiming to achieve the following: (1) assess

the impact of delayed ICU transfer on the prognosis of shock patients, (2) analyze the significance of early ultrasound-guided diagnosis and treatment within 6 hours of shock onset, (3) identify core clinical and ultrasound indicators associated with shock management and outcomes, and (4) investigate the relationship between suboptimal treatment practices in general wards and patient outcomes. These objectives are aimed at providing essential evidence to support the subsequent development of the OPACCUS protocol—a visual shock management system designed to enhance diagnosis and treatment strategies for shock patients.

Through a comprehensive analysis of clinical data, this research explores the association between ICU transfer delays and key outcomes such as survival rates, disease severity, and other critical clinical indicators. The findings emphasize the importance of timely ICU admission and early diagnostic interventions, such as ultrasound, in managing shock. Furthermore, this study offers a solid foundation for optimizing early diagnostic and therapeutic strategies, ultimately contributing to improved survival rates and advancing shock management protocols in clinical practice.

1.7.2 Research Innovations

1) **Systematic study of the prognostic impact of delayed transfer of shock:** This research stands out as a pioneering effort to systematically assess the specific impact of delayed transfers from the general ward to the ICU on the prognosis of shock patients. By conducting a detailed analysis across different transfer time groups, the study reveals how delays affect survival rates, disease severity, and major clinical indicators. This new understanding highlights the crucial role that timely ICU admission plays in the management of shock, offering actionable insights for improving patient outcomes.
2) **Multi-dimensional Clinical Indicators Analysis:** In addition to examining mortality rates, this study incorporates a broad range of key clinical indicators, including lactate levels, blood creatinine, platelet counts, and troponin T levels. By adopting this comprehensive, multi-dimensional approach, the research provides deeper insights into how early interventions influence patient outcomes. This analysis adds complexity to the traditional focus on survival,

offering a more holistic view of effective shock management.

3) **Comparison of Intervention Effects Across Time Groups:** This study innovatively compares interventions across different transfer time groups, demonstrating how early ICU transfer affects the use of mechanical ventilation, ultrasound, antibiotics, and vasoactive drugs. By doing so, the research offers crucial evidence on the clinical effectiveness of early interventions and their ability to improve prognosis. These comparisons help refine treatment strategies and optimize care for shock patients.
4) **Incorporation of Latest Research and Guidelines:** The study integrates the latest advances in early goal-directed therapy and lactate level monitoring, applying these principles across different transfer time groups. This not only validates existing clinical practices but also introduces new evidence to guide the evolution of treatment protocols in critical care. This approach keeps the research aligned with cutting-edge methodologies, ensuring its relevance in modern clinical settings.
5) **Empirical Support for Optimizing Clinical Practice (4+1):** One of the key contributions of this research lies in its ability to provide empirical evidence for optimizing shock management practices. By addressing four core areas—delayed ICU transfer, early ultrasound-guided diagnosis and treatment, identification of core clinical and ultrasound indicators, and the relationship between suboptimal general ward care and prognosis—this study presents a well-rounded framework for enhancing shock treatment. Additionally, the research lays the groundwork for the development and validation of the OPACCUS protocol, a visual management system that aims to further improve diagnostic accuracy and treatment efficiency in critical care. These innovations collectively support a significant advancement in clinical decision-making and patient outcomes.

Value of 4+1 Research Objectives: The "4+1" research objectives are critical in demonstrating the value of this study. By systematically addressing the timing of ICU transfers, the importance of early ultrasound, and identifying key clinical indicators, the study offers a foundation for improving the early management of shock patients.

These efforts not only optimize current treatment practices but also pave the way for future innovations like the OPACCUS protocol. This comprehensive approach significantly enhances the clinical understanding of shock treatment, ultimately contributing to more precise, evidence-based critical care protocols.

2. Prognostic Impact of a New Visualized OPACCUS Diagnostic and Therapeutic Assessment Process for Shock Based on Etiology, Hemodynamics, and Organism Response

Shock is a common acute and critical condition in the intensive care unit that can lead to severe consequences or even death if not managed promptly. However, the current approaches to diagnosing and treating shock face numerous challenges, particularly regarding timeliness and standardization [89, 122, 123]. Clinically, shock is often recognized by hypotension, but this method is frequently accompanied by the issue of false alarms. This can lead to alarm fatigue among healthcare providers, potentially causing them to miss critical opportunities for intervention. Moreover, during the onset and resuscitation of shock, patients' conditions can change rapidly, necessitating real-time monitoring of multiple indicators for a comprehensive assessment [124, 125]. Unfortunately, patient data are often fragmented across different healthcare information systems, increasing the cognitive burden on physicians and potentially delaying treatment.

To address these challenges, we designed a multicenter prospective real-world study with a predefined expert-guided protocol to train intensivists and promote the use of the OPACCUS diagnostic protocol. The aim of this study was to validate the effectiveness of the OPACCUS protocol in improving patient outcomes.

In this study, the implementation of OPACCUS was analyzed in 540 shock patients, who were divided into three groups based on the OPACCUS execution rate: the complete execution group (n=171, execution rate = 100%), the moderate execution group (n=149, 50% ≤ execution rate < 100%), and the low execution group (n=220, execution rate < 50%). The study results showed no significant difference in 30-day mortality between the full execution group and the medium execution group (21.05% vs. 28.86%, HR = 1.254, RMST = -3.783). However, the 30-day mortality rate was significantly lower in the full execution group compared to the low execution group

(36.82%, HR = 1.646, P < 0.05; RMST = -3.223, P < 0.05). Additionally, the survival time was 3.223 days shorter in the low execution group compared to the full execution group (95% CI: -7.549 to -1.103), and both ICU costs and total hospital costs were significantly higher. Specifically, ICU costs and total hospitalization costs were ¥46,130 (95% CI: 0.433 to 8.793) and ¥55,830 (95% CI: 0.963 to 10.202) higher, respectively, in the moderate execution group than in the full execution group.

In this study, the new OPACCUS assessment process—integrating the trinity of shock management (disease, symptoms, and organism response) with visual diagnostic tools under a novel conceptual framework—demonstrated clear advantages in managing shock patients. The process significantly improved the 30-day mortality rate of these patients. The data indicated a progressive increase in mortality rates across groups with high, medium, and low execution rates, with a statistically significant difference between the fully executed group and the low execution group. This finding suggests that the complete application of OPACCUS can markedly reduce mortality in shock patients.

Furthermore, the study confirmed the value of the OPACCUS process in the clinical management of shock. It also set a precedent for incorporating critical care ultrasound into the evaluation and analysis of shock patients, which can help reduce physician errors and enhance application efficiency.

This is the first structured process designed to evaluate shock patients using a predefined expert protocol that combines critical care ultrasound with clinical data. It aims to study the impact of the OPACCUS assessment protocol on patient outcomes as utilized by critical care physicians. The OPACCUS protocol, developed by a team of experienced experts, is built on a model that considers the trinity of disease, symptoms, and organism response in shock management: first, identifying the primary cause [37, 126] (such as infection, hemorrhage, trauma, obstruction, or myocardial damage); second, determining the type of dysregulated organism response (such as autonomic dysregulation due to overstress, immune-inflammatory dysregulation due to an inflammatory storm, hypercoagulability/thrombosis leading to coagulation abnormalities, and bioenergetic imbalance caused by cellular mitochondrial dysfunction); and finally, identifying the phenotype of hemodynamic disturbances

(such as vascular tone, resistance, cardiac output, and venous stasis)[13, 127, 128].

In the management of shock, ultrasound assessment has demonstrated significant advantages in evaluating cardiac function, organ perfusion, and vascular tone. The 2014 European Society of Intensive Care Medicine guidelines recommended echocardiography as the preferred method for assessing shock types, although these guidelines did not provide detailed instructions on its specific application [10]. Similarly, the 2016 International Federation of Emergency Medicine's International Consensus Guidelines on bedside ultrasound for managing hypotension only offered general recommendations [43, 129]. While several studies have not clearly established a relationship between the use of critical care ultrasound and patient outcomes in shock [130], research by Kanji et al. has shown that echocardiography can help reduce mortality in shock patients [58]. Despite existing studies focusing on the role of critical care ultrasound in shock management, there remains a lack of a standardized process that integrates assessment and analysis to clarify the relationship between shock treatment and patient prognosis.

Our study demonstrated significantly improved outcomes in patients with higher adherence to the OPACCUS protocol. This finding not only confirms the value of the OPACCUS process but also, for the first time, integrates critical care ultrasound into the assessment and analysis framework, helping to reduce misdiagnosis and mistreatment by physicians and improving diagnostic and treatment efficiency. Ultrasound assessment can effectively meet the information needs at each stage of diagnosis and treatment, including non-invasive and efficient evaluation of the patient's baseline status, primary lesions, systemic responses, and hemodynamic phenotypes[131-133]. Building on this foundation, the Critical Care Hemodynamic Therapy Collaborative Group and the Critical Care Ultrasound Visualization Research Group have established a visual, refined, and modular monitoring system based on critical care ultrasound, further developing the concept of ultrasound hemodynamics.

By incorporating critical care ultrasound into diagnostic and treatment protocols, we can simultaneously monitor systemic circulation, microcirculation, oxygen metabolism, as well as primary and excessive systemic responses. This allows the establishment of a comprehensive OPACCUS diagnostic and treatment protocol for

etiological screening and management, systemic response modulation, and refined hemodynamic management. Such integration helps to correct the imbalance between oxygen supply and demand, improving the pathophysiological state of the systemic circulation and thereby optimizing the outcomes for patients in shock.

The reason why some of the partially implemented groups in the study did not show improvement over the low implementation group may be due to several factors:

First, this is a real-world study rather than a prospective randomized controlled trial (RCT), leading to insufficient differentiation between the medium and low implementation groups.

Second, regarding the criteria for defining the medium and low groups, we grouped these based on usage frequency. However, this categorization was artificially set by us, and the actual clinical needs of each patient can vary significantly. As a result, the grouping may not have effectively distinguished between the clinical benefits of medium-frequency use and low-frequency use.

Despite this, we did confirm that the full implementation group performed significantly better than the medium and low groups. Physicians who fully adhered to the OPACCUS protocol had better outcomes than those who partially used critical care ultrasound, highlighting the value of the OPACCUS process.

In this study, due to the fact that the OPACCUS implementation rate subgroups did not meet the Cox proportional hazards (PH) assumption and showed a delayed effect, the Max Combo test was used instead of the log-rank test, and Fleming test values were provided. The Max Combo test is a weighted log-rank test designed for combinations of multiple Fleming-Harrington (FH) (p, v) settings[134]. It estimates the test statistic Z separately for each of the four weight combinations—FH(0,0), FH(0,1), FH(1,0), and FH(1,1)—and the maximum value of Z is taken as the final test conclusion, i.e., Zmax = max(|Z1|, |Z2|, |Z3|, |Z4|). The advantage of the Max Combo test is its ability to control Type I error effectively while maintaining robustness across different non-proportional hazard scenarios.

Additionally, we conducted a landmark-Kaplan-Meier (KM) analysis to mitigate the bias that might arise from subjectively chosen cut-off points. For subsequent multivariate analyses, we used the classical Restricted Mean Survival Time (RMST)

inverse probability weighting model, which does not require the PH assumption. This model has been used in numerous previous studies for survival data with delayed effects. To ensure the generalizability of our study, we ultimately adopted a multifactorial analysis strategy combining both RMST and Cox regression.

Limitations of our study include:

Firstly, this is a real-world study, not a rigorously designed RCT, so there might be controversy over the grouping criteria during statistical analysis. However, we critically assessed the degree of protocol implementation via an information platform, allowing us to refine the full, medium, and low implementation groups. Moreover, in the multicenter study, the proficiency of clinicians from different centers in mastering the OPACCUS protocol may vary, but it is difficult to assess this indicator.

Secondly, we cross-validated the outcomes using different statistical methods, confirming the value of full implementation.

Thirdly, as this study investigates protocol adherence behavior, using an RCT design could potentially result in cross-contamination between groups due to compliance issues, thereby obscuring the value of validating the protocol.

Fourthly, this is a diagnostic and treatment protocol study. From ethical and medical safety perspectives, the decision to implement the protocol rests with the attending physician, making a strict RCT design inappropriate.

Fifthly, although this study is based on ultrasound evaluations, it lacks corresponding ultrasound images and specific ultrasound data analyses. This may limit readers' intuitive understanding of the role of ultrasound in the diagnosis and treatment of shock, affecting the comprehensiveness and persuasiveness of the study results. This study can serve as a reference; future research can delve deeper by adding ultrasound images and detailed data analyses to enhance the depth and credibility of the research.

Lastly, through our real-world study and robust statistical analysis, we have validated our research expectations and achieved the anticipated results. In future studies, we plan to expand the sample size and enhance real-time monitoring of protocol adherence to further confirm the value of our current findings.

Future research should also continue to explore ways to improve adherence to the

OPACCUS protocol. This may involve training and real-time feedback mechanisms to enhance healthcare professionals' application of standardized diagnostic and therapeutic processes. We believe that with further research and optimization, the OPACCUS protocol will provide better treatment options for shock patients and improve clinical outcomes.

Conclusions

This study highlights the critical importance of early transfer to the ICU for improving the prognosis of shock patients. The results from the first part show that delaying the transfer by more than six hours significantly increases mortality risk. Therefore, early identification and timely ICU transfer are essential for enhancing the survival rates of shock patients. Additionally, the early use of ultrasound in shock management further improves patient outcomes. The in-hospital mortality prediction model developed in this study demonstrates good discrimination and calibration, providing significant clinical utility. The findings offer robust evidence supporting the optimization of early intervention strategies, suggesting that clinical practice should focus on reducing the time between initial diagnosis in general wards and transfer to the ICU, while incorporating ultrasound assessments.

The second part of the study validated the effectiveness of the OPACCUS protocol, based on ultrasound visualization, in ICU settings. The results demonstrate that the OPACCUS protocol significantly improved survival rates, reduced ICU length of stay, and lowered hospital costs. Higher adherence to the OPACCUS protocol is strongly associated with better survival outcomes, underscoring its effectiveness and potential for widespread use in personalized shock management. Future studies should focus on further optimizing and expanding the protocol to encompass a broader patient population, with the goal of improving the precision and efficiency of shock management.

Supplementary Legends

Table S1: APACHE II Score Physiologic Variables Points

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	4	3	2	1	0	1	2	3	4
Temperature - rectal (º C)	> 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	< 29.9
MAP (mmHg)	> 160	130-159	110-129		70-109		50-69		< 49
Heart Rate	> 180	140-179	110-139		70-109		55-69	40-54	< 39
Respiratory Rate (non-ventilated or ventilated)	> 50	35-49		25-34	12-24	10-11	6-9		< 5
Oxygenation: [A-aDO2 = (FiO2 x 710) – (PCO2 x 1.25) – PO2]									
a. FiO2 > 0.5 record A-aDO2	> 500	350-499	200-349		< 200				
b. FiO2 < 0.5 record only PaO2					PaO2>70	PaO261-70		PaO255-60	PaO2 < 55
Arterial pH	> 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
Serum Na (mmol/L)	> 180	160-179	155-159	150-154	130-149		120-129	111-119	< 110
Serum K (mmol/L)	> 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
Creatinine (umol/L)	> 305	170-304	130-169		53-129		<53		
Hematocrit (%)	> 6		50-59.9	46-49.9	30-45.9		20-29.9		< 20
WBC (total/mm^3)	> 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1
Glasgow Coma Score (GCS)	Score = 15 minus actual GCS (see below)								
HCO3 (venous mmol/L) - not preferred, use if no ABGs	> 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.0	< 15

Creatinine Double Points for Acute Renal Failure

Acute Physiology Score (APS): Sum of the 12 individual variable points

A. Age Points

- Assign points based on the patient's age as follows:

AGE (year)	AGE SCORE
< 44	0
45-54	2
55-64	3
65-74	4
> 75	5

C. Chronic Health Points

- Assign points based on the patient's history of severe organ system insufficiency or immunocompromised status as follows:

a. Non-operative or emergency post-operative patient — 5 points

b. Elective post-operative patient — 2 points

D. APACHE II Score = A + B + C

Chronic Health Definitions

Organ insufficiency or immunocompromised state must have been evident prior to this hospital admission and meet the following criteria:

LIVER: Biopsy-confirmed cirrhosis with documented portal hypertension, prior episodes of upper gastrointestinal bleeding due to portal hypertension, or previous episodes of hepatic failure, encephalopathy, or coma.

CARDIOVASCULAR: New York Heart Association (NYHA) Class IV heart failure.

RESPIRATORY: Severe chronic restrictive, obstructive, or vascular lung disease causing significant exercise limitation (e.g., inability to climb stairs, perform activities of daily living, or household chores); or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or ventilator dependence.

RENAL: Receiving chronic dialysis

IMMUNO-COMPROMISED: The patient has received treatments that suppress immune resistance to infection, such as immunosuppressive therapy,

chemotherapy, radiation, or long-term or recent high-dose corticosteroids. Alternatively, the patient has an advanced disease that suppresses immune resistance, such as leukemia, lymphoma, or AIDS.

Table S2: Sequential Organ Failure Assessment (SOFA) Score

Organ System	Measurement	SOFA Score				
		0	1	2	3	4
Respiration	PaO2/FiO2,mmHg	>400	<400	<300	<200	<100
	Respiratory support	no	no	no	yes	yes
Coagulation	Platelet,10^9/L	>150	101-150	51-100	21-50	<21
Liver	Bilirubin, μmol/l	<20	20-32	33-101	102-204	<204
Cardiovascular	Hypotension	Normal	MAP<70mmHg	Dopamine <5 or dobutamine (any dose)**	Dopamine >5 or epinephrine <0.1 or norepinephrine <0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system	Glasgow ComaScore	Normal	13-14	10-12	6-9	<6
Renal	Creatinine, mg/dL (μmol/l) Or Urine output	Normal	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500 mL/day	>5.0 (>440) or <200 mL/day

Note: **Adrenergic agents administered for at least 1 hour (doses given are in mcg/kg/min).

Table S3: GLASGOW COMA SCALE (GCS) score

Parameter	Response	Points assigned
Eye-opening	Spontaneous	4
	Response to verbal command	3
	Response to pain	2
	No eye opening	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal response	1
Best motor response	Obeys commands	6
	Localizing response to pain	5
	Withdrawal response to pain	4
	Flexion to pain	3
	Extension to pain	2
	No motor response	1

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Literature review

Evolutionary Pattern of Septic Shock and Early Treatment Strategy

NGAN CHANSOKHON Reviewed by YAN KANG

Introduction

Sepsis is a life-threatening condition characterized by a systemic inflammatory response syndrome (SIRS) triggered by a dysregulated host response to infection[1-5]. Its hallmark features include multiple organ dysfunction, a wide spectrum of clinical manifestations, and a high incidence of both morbidity and mortality, all of which contribute to the complex challenges of clinical management. In recent years, evolving definitions of sepsis have further emphasized the abnormal host response as the key driver of infection-induced multi-organ dysfunction, leading to potentially life-threatening conditions[6, 7]. With growing insights into the pathophysiology of sepsis, guidelines for its diagnosis, treatment, and prognosis have continuously been refined and improved.

As sepsis progresses, it can culminate in septic shock—a severe and often fatal form of sepsis characterized by profound hemodynamic abnormalities, including persistent hypotension and inadequate tissue perfusion[8-11]. Globally, sepsis has an incidence rate of approximately 30%, with a mortality rate of around 10%[12]. In contrast, septic shock has a mortality rate exceeding 40%, making it one of the most critical conditions encountered in intensive care units (ICUs)[13, 14]. The conceptual framework of sepsis and septic shock has undergone significant evolution, transitioning from an initial focus on systemic inflammatory response to a more nuanced understanding that incorporates the complex interplay of pathogen-induced host responses.

Recent advancements in medical research have uncovered that the pathogenesis of septic shock involves a multifaceted dysregulation of the immune system. This dysregulation triggers a cascade of events, including the release of inflammatory

mediators, endothelial dysfunction, impaired microcirculation, and ultimately, multiple organ failure [15]. The intricate nature of this pathological process presents substantial challenges in the early diagnosis and timely management of septic shock[16-20]. Despite considerable progress in the early recognition and intervention of septic shock, numerous questions remain unanswered, highlighting the need for ongoing research and innovation in this field[21].

The evolution of our understanding of septic shock mirrors the broader advancements in sepsis research. Initially, sepsis was defined primarily by the systemic inflammatory response to infection. However, as medical science has advanced, a more comprehensive understanding has emerged, one that encompasses immune dysregulation, hemodynamic instability, microcirculatory dysfunction, and their collective impact on multiple organ systems. These insights have informed the optimization of therapeutic strategies and the development of more sophisticated clinical guidelines[22-25]. The 2016 Sepsis-3 Consensus further clarified the definitions of sepsis and septic shock, placing greater emphasis on the host's dysregulated response to infection and the associated potential for rapid clinical deterioration[13, 21, 26-28]. This consensus has provided the medical community with updated guidelines that are critical for improving clinical outcomes is shown in Figure 1-2.

This review seeks to explore the evolution of septic shock and the strategies for early treatment, with a focus on several key areas: early localization and drainage of infectious foci, rapid identification of pathogens, rational antibiotic use, modulation of the inflammatory response, hemodynamic support, the role of artificial intelligence in enhancing clinical decision-making, and the application of genomics in precision medicine. By systematically analyzing and synthesizing the existing body of research, this review aims to offer new insights and strategies for the early diagnosis and management of septic shock, ultimately striving to improve patient outcomes and reduce mortality.

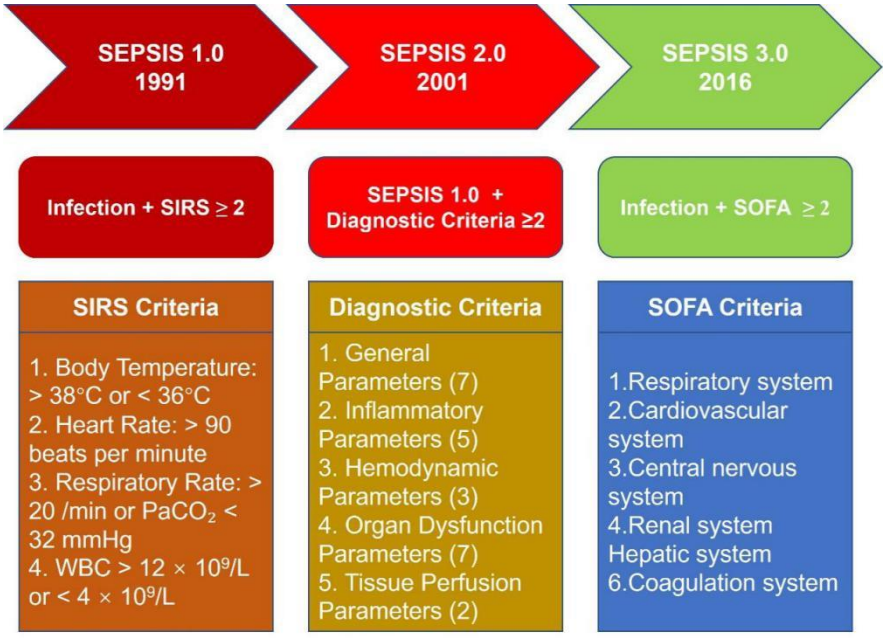

Figure 1: The Evolution of Definitions for Sepsis and Septic Shock

Note: SIRS, Systemic Inflammatory Response Syndrome; WBC, White Blood Cell counts; SOFA, Sequential Organ Failure Assessment.

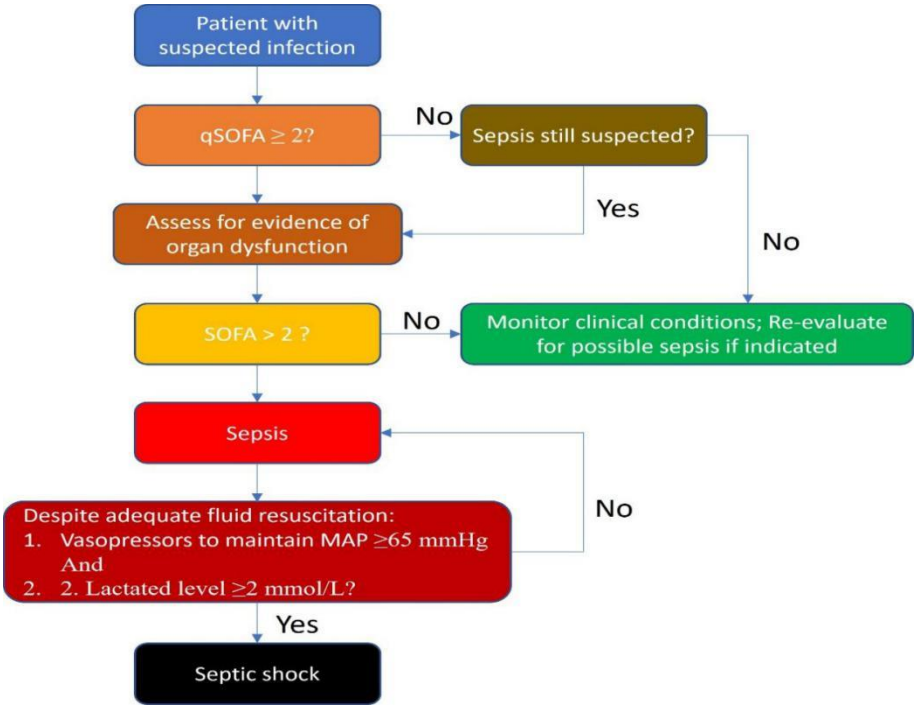

Figure 2: Flowchart of Clinical Diagnostic Criteria for Sepsis and Septic Shock

Note: qSOFA, quick Sequential Organ Failure Assessment; MAP, Mean Arterial Pressure.

1. Early Localization and Drainage of Lesions (Ultrasound)

Effective management of septic shock hinges on the prompt and accurate control of the infection source. Without addressing the underlying infection, successful treatment of septic shock is nearly impossible. Early and precise localization of infected foci is paramount in guiding antimicrobial therapy, surgical drainage, and subsequent treatment, ultimately improving patient prognosis and reducing mortality rates[29-31]. The importance of this is underscored by studies highlighting the higher incidence of combined sepsis and metastatic infections in patients with specific conditions, such as Klebsiella liver abscess, where vigilant monitoring and control of sepsis spread are crucial[32].

Ultrasonography stands out as a non-invasive, rapid, and readily accessible imaging modality that plays a critical role in the localization and drainage of septic foci, particularly in patients with septic shock[33]. In such patients, the infection may be multifocal, involving organs such as the lungs, abdominal cavity, urinary system, or soft tissues. For instance, in cases of pulmonary infections, ultrasound is highly effective in identifying solid lung lesions, pleural effusions, and pyothorax. It is notably more sensitive than conventional chest radiographs and even CT scans in detecting pleural effusions. This superior sensitivity is vital in guiding timely interventions, such as thoracentesis or chest tube placement, which can be life-saving.

Moreover, ultrasound's utility extends beyond pulmonary applications. It is invaluable in diagnosing and managing intra-abdominal infections, such as abdominal abscesses, liver abscesses, cholecystitis, pancreatitis, and bowel perforation. Ultrasound can guide real-time puncture or surgical drainage, ensuring precise and effective treatment. A notable study demonstrated that ultrasound-guided surgical drainage of abscesses in rectal fistulae was more effective than traditional methods, leading to better outcomes[34]. Additionally, another study confirmed the efficacy of ultrasound in guiding life-saving interventions such as bile duct decompression, which not only shortens procedure time but also prevents complications like pancreatitis following endoscopic retrograde cholangiographic stent placement. So ultrasound serves as an indispensable tool in the early localization and drainage of lesions in septic

shock patients, significantly contributing to improved outcomes and reduced mortality.

2. Rapid pathogen identification (PCR/mNGS)

In the management of septic shock, the rapid and accurate identification of causative pathogens is crucial for developing an effective and targeted anti-infective treatment regimen. The urgency of this process cannot be overstated, as delays in appropriate antimicrobial therapy are directly associated with increased mortality. A meta-analysis by Valentino et al. underscores the critical need for rapid microbiological diagnosis to facilitate early, targeted antimicrobial therapy in sepsis[35]. Traditional microbiological culture methods, while reliable, typically require several days to yield results—a timeframe that is often too slow for patients in acute, life-threatening conditions such as septic shock.

In this context, advanced technologies like PCR (polymerase chain reaction) and mNGS (metagenomic next-generation sequencing) have emerged as powerful tools in the rapid identification of pathogens. These technologies significantly reduce the time required for pathogen detection and provide more comprehensive and accurate diagnostic information.

PCR is a molecular biology technique that amplifies specific DNA fragments with high sensitivity and specificity[36]. By detecting even minute amounts of pathogenic DNA, PCR can identify pathogens within hours, offering a critical advantage in the early stages of septic shock management[37, 38]. This rapid identification enables clinicians to initiate targeted antimicrobial therapy much earlier than would be possible with conventional culture methods.

mNGS, on the other hand, is a high-throughput sequencing technology that can sequence and analyze all genomic DNA present in a sample. Unlike traditional targeted assays, mNGS does not rely on specific primers and is capable of identifying a broad spectrum of pathogens, including bacteria, viruses, fungi, and parasites—whether known or previously unidentified[39, 40]. A study that applied mNGS to monitor 52 out of 386 cases of unexplained sepsis (13%) successfully identified 21 viruses known to infect humans, demonstrating the technology's potential to uncover hidden or unexpected pathogens[41]. The application of PCR and mNGS technologies in septic

shock management extends to several critical areas:

Early Diagnosis: By rapidly detecting and identifying pathogens, PCR and mNGS can provide crucial pathogen information early in a patient's hospital admission. This early detection allows for the timely initiation of targeted therapy, which is essential for improving outcomes in septic shock.

Identification of Complex Infections: In cases involving mixed multi-pathogen infections or infections caused by rare or atypical pathogens, mNGS can offer a comprehensive pathogenic spectrum. This capability helps clinicians make accurate diagnoses and tailor treatment strategies to address the full range of infectious agents involved.

Antibiotic Adjustment: Based on the results from PCR and mNGS, clinicians could adjust antibiotic types and dosages in real-time to optimize the treatment plan. This approach not only enhances the effectiveness of the therapy but also helps prevent the misuse of broad-spectrum antibiotics, thereby reducing the risk of developing drug-resistant strains.

So the integration of PCR and mNGS technologies into the management of septic shock represents a significant advancement in the field of infectious disease diagnostics. These tools enable rapid, precise pathogen identification, which is essential for guiding early and effective treatment, ultimately improving patient outcomes and reducing mortality.

3. Rational Use of Antibiotics

In the treatment of sepsis and septic shock, the rational and judicious use of antibiotics is a cornerstone of effective management, yet the timing and selection of antibiotics remain subjects of ongoing debate and research[42, 43]. Timely empirical antibiotic therapy that effectively targets potential pathogens is critical for the successful treatment of septic shock. Multiple studies have confirmed that delays in initiating appropriate antibiotic therapy are associated with significantly worse outcomes, including increased hospital mortality and prolonged length of hospital stay[44-47]. The Surviving Sepsis Campaign (SSC) guidelines advocate for the administration of antibiotics within one hour of sepsis onset[27]. However,

implementing such a short timeframe in clinical practice can be challenging[48, 49], and the evidence supporting the one-hour goal remains inconclusive. Consequently, organizations such as the Society of Critical Care Medicine and the American Academy of Emergency Medicine have issued a joint statement advising against a rigid one-hour target, instead promoting flexibility based on individual patient circumstances[50].

Selecting the appropriate antibiotic regimen—considering factors such as the correct dosage and administration schedule—not only facilitates rapid infection control but also minimizes the risk of antibiotic resistance, reduces adverse effects, and improves overall treatment outcomes [51, 52]. In the initial stages of septic shock, immediate empirical therapy with broad-spectrum antibiotics is often necessary, as the causative pathogen has not yet been identified. Several key considerations should guide the selection of antibiotics:

Pathogen Coverage: Broad-spectrum antibiotics should be chosen to cover a wide range of potential pathogens, including common Gram-positive and Gram-negative bacteria, anaerobes, fungi, and other likely culprits.

Site of Infection: The choice of antibiotics should be tailored to the likely pathogens associated with the specific site of infection. For example, lung infections may require different coverage than intra-abdominal or urinary tract infections.

Patient History: A thorough review of the patient's previous infections, antibiotic use, and any history of drug allergies is essential to avoid adverse reactions and to ensure the selection of an effective antibiotic.[53].

The use of inappropriate antibiotics could have dire consequences, with studies indicating that it may increase mortality by up to 30%[54, 55]. Once pathogen identification and sensitivity testing results are available, the antibiotic regimen should be adjusted to target the specific pathogens involved, typically by switching to narrower-spectrum antibiotics. This approach helps to avoid the unnecessary use of broad-spectrum antibiotics and reduces the risk of developing antibiotic resistance.

Rational Antibiotic Dose Management

Rational management of antibiotic dosing is crucial to ensure therapeutic efficacy

while minimizing the risk of adverse effects[56]. This involves several strategies:

Initial High-Dose Therapy:

In the acute phase of septic shock, high doses of antibiotics are often necessary to rapidly achieve effective blood concentrations and control the infection[57].

Pharmacokinetic and Pharmacodynamic (PK/PD) Considerations:

Antibiotic dosing should be based on PK/PD properties. For example, time-dependent antibiotics like β-lactams require sustained blood concentrations, while concentration-dependent antibiotics like aminoglycosides require peak concentrations to be effective[58].

Renal and Hepatic Function Monitoring:

Patients with septic shock often experience renal and hepatic dysfunction, necessitating careful monitoring and dose adjustments to avoid drug accumulation and toxicity[59, 60].

Antibiotic Resistance and Stewardship

Antibiotic resistance is a significant challenge in the treatment of septic shock, and managing this risk is an integral part of antibiotic therapy[61]. Key strategies include:

Regular Drug Sensitivity Testing:

Especially when clinical improvement is not observed, regular sensitivity testing helps assess pathogen resistance and informs timely adjustments to the antibiotic regimen[62].

Management of Multidrug-Resistant Bacteria (MDR):

For infections involving MDR organisms, targeted antibiotics should be used alongside stringent infection control measures to prevent the spread of resistant strains[63].

Antibiotic Stewardship Programs (AMS):

Hospitals should implement AMS programs to promote the rational use of antibiotics, monitor resistance trends, and provide ongoing training for healthcare providers[64].

Optimizing the Antibiotic Regimen

Optimizing antibiotic therapy involves rational combinations, careful

management of treatment duration, and timely discontinuation:

Antibiotic Combinations:

In certain cases, combining antibiotics, such as β-lactams with aminoglycosides, could broaden the antimicrobial spectrum, enhance bactericidal efficacy, and reduce the risk of resistance[65].

Course Management:

The duration of antibiotic therapy should be as short as possible to minimize adverse effects and resistance, yet long enough to ensure adequate infection control[66].

Discontinuation of Antibiotics: Antibiotics should be discontinued once clinical improvement is evident and infection markers (e.g., C-reactive protein, white blood cell count) have returned to normal levels. This practice helps avoid the negative consequences of prolonged antibiotic use.

So, the rational use of antibiotics in septic shock requires a balance between timely intervention and careful management of antibiotic selection, dosing, and duration. By adhering to these principles, clinicians can optimize treatment outcomes, reduce the risk of resistance, and improve patient survival rates.

4. Inflammation Management

The management of inflammation in patients with septic shock is a complex and nuanced process, as the inflammatory response is heterogeneous, with patients exhibiting distinct inflammatory phenotypes and molecular profiles[67]. Understanding these differences is crucial for developing individualized treatment plans that can effectively address the specific needs of each patient.

Inflammatory Phenotypes and Molecular Typing

Inflammatory phenotypes refer to the varying clinical manifestations of the inflammatory response in patients[8]. Some patients exhibit a high-inflammatory phenotype characterized by an exaggerated immune response, while others display a low-inflammatory phenotype, marked by a subdued inflammatory reaction. Patients with a high-inflammatory phenotype may benefit from more aggressive anti-inflammatory therapies, whereas those with a low-inflammatory phenotype must avoid excessive suppression of inflammation, which could compromise their immune

defense[30, 68]. Molecular typing involves the analysis of molecular markers in a patient's blood or tissues—such as cytokines, chemokines, and acute-phase proteins—to accurately identify the specific type of inflammation present[69, 70]. This molecular-level information allows for a more precise assessment of the patient's inflammatory state, guiding the selection of appropriate, individualized treatment strategies.

Anti-Inflammatory Drugs and Immunomodulators

The choice of anti-inflammatory drugs and immunomodulators should be tailored based on the patient's inflammatory phenotype and molecular profile. Commonly used anti-inflammatory medications include glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) [71-73]. Glucocorticoids are potent anti-inflammatory agents that reduce the inflammatory response by inhibiting the release of pro-inflammatory mediators, making them particularly useful for patients with a hyperinflammatory phenotype[74]. However, the use of glucocorticoids must be approached with caution due to their potential to cause immunosuppression and increase the risk of secondary infections[1]. NSAIDs, on the other hand, work by inhibiting cyclooxygenase (COX) enzyme activity, thereby reducing the synthesis of pro-inflammatory prostaglandins[71, 75]. Immunomodulators are another class of drugs that play a crucial role in controlling inflammation by modulating specific immune pathways. Examples include interleukin-6 (IL-6) receptor antagonists and tumor necrosis factor (TNF) inhibitors[76]. These targeted therapies can be particularly effective in patients whose molecular typing indicates a specific inflammatory pathway is driving their condition[77, 78].

Individualized Therapeutic Strategies

The development of individualized therapeutic strategies involves creating treatment plans tailored to the unique inflammatory phenotype and molecular profile of each patient. For example, one study found that discontinuation of antibiotics in septic patients could be considered when procalcitonin (PCT) levels fall below 0.5 μg/L[79]. However, another study suggested that in some septic patients, prolonged antibiotic use based on PCT levels was associated with higher mortality[80]. Therefore, the duration of antibiotic therapy in sepsis should not be determined solely by PCT levels

but should also consider the patient's inflammatory phenotype, molecular typing, and other clinical and biological factors.

Given that the inflammatory state of patients with septic shock can evolve over the course of the illness, continuous monitoring and dynamic assessment are essential. Regular measurement of inflammatory markers such as PCT, C-reactive protein (CRP), white blood cell count, and cytokine levels helps to assess the effectiveness of treatment and allows for timely adjustments to the therapeutic regimen.

Multidisciplinary Team Collaboration

Effective inflammation management in septic shock requires the collaboration of a multidisciplinary team, including intensivists, immunologists, pharmacists, and other specialists[67]. This collaborative approach ensures that all aspects of the patient's condition are considered and that the treatment plan is optimized by integrating the expertise and perspectives of various disciplines. By working together, the team can develop and implement a comprehensive and effective inflammation management strategy, improving outcomes for patients with septic shock.

5. Hemodynamics (Oxygen Therapy-Oriented/Typing-Oriented)

Effective hemodynamic management is critical in the treatment of sepsis and septic shock, as it plays a pivotal role in improving tissue perfusion, preventing organ failure, and significantly enhancing patient survival[81-83]. Two primary strategies in hemodynamic management—oxygen therapy-oriented and typing-oriented—focus on initial resuscitation, goal-directed therapy, hemodynamic monitoring, and individualized treatment plans[68].

Initial Resuscitation and Fluid Management

Patients with septic shock typically present with hypotension and inadequate tissue perfusion, necessitating rapid fluid resuscitation and vasopressor therapy to restore hemodynamic stability[84, 85]. Fluid resuscitation is an essential intervention aimed at increasing venous return, cardiac output (CO), and oxygen delivery[86]. The key to successful fluid resuscitation lies in administering an adequate volume and duration of fluids while closely monitoring the patient to prevent fluid overload[87]. During the initial resuscitation phase, the rapid infusion of isotonic crystalloid

solutions, such as saline or lactated Ringer's solution, is recommended. Previous guidelines emphasized early goal-directed therapy (EGDT), with resuscitation goals set within the first six hours, including central venous pressure (CVP) of 8-12 mmHg, mean arterial pressure (MAP) >65 mmHg, urine output >0.5 mL/kg/h, and central venous oxygen saturation (ScvO2) >70% or mixed venous oxygen saturation (SvO2) >65%[88-90]. The primary objective is to restore effective circulating blood volume and enhance tissue perfusion.

The Surviving Sepsis Campaign (SSC) adult guidelines advocate for immediate initiation of resuscitation following the diagnosis of septic shock, recommending the infusion of at least 30 mL/kg of fluids over the course of three hours, accompanied by close monitoring of the patient's response[91, 92]. If hypotension persists after adequate fluid resuscitation, prompt administration of vasopressors is necessary, with norepinephrine being the first-line agent of choice due to its effectiveness in increasing vascular resistance and cardiac output [92-94].

Hemodynamic Monitoring and Goal-directed Therapy

Achieving optimal goal-directed therapy hinges on effective hemodynamic monitoring. Continuous assessment of hemodynamic parameters enables timely adjustments to the treatment plan, ensuring the best possible therapeutic outcomes. Basic monitoring tools include continuous electrocardiogram (ECG) monitoring, non-invasive blood pressure monitoring, and pulse oximetry, all of which provide essential information about cardiovascular status. In critically ill patients, advanced monitoring techniques such as arterial catheterization, central venous catheter monitoring, pulse contour analysis, and echocardiography may be required. These advanced tools offer more detailed hemodynamic data, including cardiac output, central venous pressure, and arterial pressure waveform analysis, allowing for a more nuanced understanding of the patient's condition.

Typing-Oriented Hemodynamic Management

The hemodynamic profile of septic shock patients is highly heterogeneous, with different individuals displaying distinct hemodynamic patterns[95]. Typing-oriented management strategies help to tailor treatment plans according to the specific

hemodynamic characteristics of each patient.

Hyperdynamic Shock: This type is characterized by high cardiac output and low systemic vascular resistance. Treatment focuses on increasing vascular resistance through the use of vasopressors, such as norepinephrine, while avoiding excessive fluid administration, which could exacerbate the condition[96, 97].

Hypodynamic Shock: In contrast, hypodynamic shock presents with low cardiac output and relatively high systemic vascular resistance. Management strategies for this type of shock involve increasing cardiac output through fluid resuscitation and the use of positive inotropic agents like dobutamine[98, 99].

Mixed Shock: This type is marked by a combination of hyperdynamic and hypodynamic features, resulting in complex hemodynamic changes. Treatment for mixed shock requires a balanced approach that includes fluid resuscitation, vasopressors, and positive inotropic agents to address the multifaceted nature of the hemodynamic instability[100]. By employing both oxygen therapy-oriented and typing-oriented strategies, clinicians can provide more individualized and effective hemodynamic management for patients with septic shock, ultimately improving outcomes and reducing the risk of organ failure and mortality.

6. Applications of Artificial Intelligence (AI)

As medical technology and data science advance, artificial intelligence (AI) has emerged as a promising tool in the diagnosis, prognosis, and treatment of critical illnesses, including sepsis and septic shock [101, 102]. AI technologies can significantly enhance patient outcomes by analyzing large volumes of clinical data, identifying complex pathological patterns, and providing personalized treatment recommendations (see Figure 3).

Early Diagnosis and Prediction

Retrospective studies have demonstrated that AI's ability to continuously monitor clinical data can predict the onset of sepsis hours in advance with an accuracy approaching 90%, a notable improvement over traditional disease severity scores [103]. Early diagnosis of septic shock is crucial for patient survival, and recent meta-analyses have shown that the benefits of AI-enabled early warning systems are particularly

pronounced in emergency departments and general wards compared to intensive care units (ICUs) [104]. By analyzing electronic health records (EHRs) and biosensor data, AI can facilitate faster and more accurate diagnoses. AI algorithms can extract and analyze vast amounts of patient information—such as medical history, laboratory results, and imaging data—from EHRs to identify risk factors and early signs of septic shock. For instance, machine learning models can assess changes in a patient's blood metrics to predict the onset of sepsis. When combined with biosensor data (e.g., from wearable devices), AI can monitor physiological parameters in real-time, such as heart rate, blood pressure, and oxygen saturation, enabling early detection of septic shock symptoms.

Personalized Treatment Recommendations

AI's ability to analyze multidimensional data allows it to offer personalized treatment recommendations and optimize treatment protocols. AI models can recommend the most appropriate treatments based on pathogenetic data, drug sensitivity tests, and the patient's clinical characteristics, ensuring timely and effective anti-infective therapy. The system can also dynamically adjust treatment plans by integrating real-time data analysis. For example, AI can suggest modifications to fluid resuscitation strategies, vasopressor dosages, or anti-inflammatory treatment regimens based on the patient's hemodynamic parameters and inflammatory markers.

Prognosis Prediction and Long-Term Management

AI's predictive capabilities extend to forecasting patient outcomes and aiding in the development of long-term management plans. A randomized controlled trial demonstrated that the use of an AI model reduced in-hospital mortality from 20% to nearly 8% and shortened the average length of hospital stay from 13 to 10 days compared to the control group [105]. By leveraging machine learning algorithms, AI can utilize a range of physiological and laboratory indicators to predict the survival chances of septic shock patients, identify high-risk individuals, and prioritize monitoring and interventions[106]. In a retrospective cohort study, machine learning models trained to predict in-hospital mortality revealed a strong association between low urine output and increased mortality in septic patients [107]. Furthermore, by

analyzing dynamic clinical data, AI can predict the risk of multi-organ failure, enabling proactive measures to reduce complications.

Real-Time Monitoring and Early Warning Systems

AI can provide early warnings to prevent condition deterioration by continuously monitoring patients' physiological parameters in real-time. When integrated with Internet of Things (IoT) technologies, AI facilitates the continuous monitoring of critically ill patients, enabling the timely detection of abnormalities and the issuance of early warning signals to healthcare professionals. Additionally, AI assistants can support caregivers in assessing patient conditions and making informed decisions, offering recommendations on medication dosages, optimizing care plans, and ultimately improving the quality and efficiency of care.

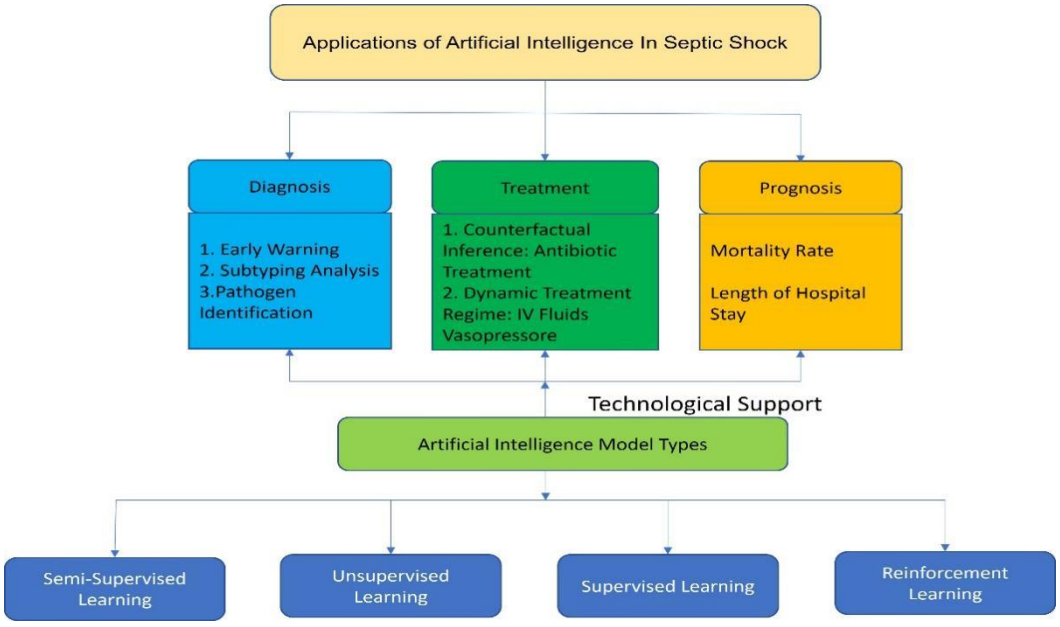

Figure 3: Overview of Artificial Intelligence Applications in Septic Shock

7. Genomics Applications

Genomics holds significant potential for advancing the study and management of septic shock[108, 109]. By analyzing a patient's genome, researchers can identify genetic variants associated with septic shock, gaining insights into an individual's genetic susceptibility. This understanding forms a crucial foundation for personalized treatment and prognostic predictions. Recent studies have employed cardiogenomic

approaches, involving DNA and RNA analysis, to uncover novel molecules, such as microbial response modulators, which could have important translational implications for sepsis treatment[110].

Genetic Susceptibility and Risk Identification

Genomic studies have shed light on genetic predispositions to septic shock, helping to identify high-risk populations. Genome-wide association studies (GWAS) have been instrumental in pinpointing genetic variants linked to septic shock[111, 112]. Several studies have demonstrated that specific single nucleotide polymorphisms (SNPs) are associated with immune responses, inflammatory modulation, and susceptibility to infections[113, 114]. Understanding these genetic risks enables the development of targeted preventive measures and early interventions. Additionally, genomic analysis of familial cases of septic shock has identified genetic susceptibility genes that may play roles in regulating the innate immune system, offering insights into disease mechanisms.

Predicting Treatment Response and Optimizing Therapeutic Strategies

Genomic analysis can also predict patient responses to different treatment regimens, thereby optimizing therapeutic strategies[115]. Gene expression profiling, which involves analyzing gene expression in peripheral blood or tissue samples, can identify genetic markers associated with treatment response. For instance, certain gene expression patterns may indicate a favorable response to immunomodulators, aiding in the identification of new therapeutic targets in sepsis pathogenesis[116]. By personalizing treatment plans based on these genetic insights, clinicians can improve patient outcomes.

Genetic Markers of Drug Response

Research has shown that specific gene variants can influence how patients respond to certain drugs. For example, recent experimental studies suggest that variants in the TLR4 gene may affect a patient's sensitivity to antibiotic therapy[117, 118]. By detecting these genetic markers, clinicians can predict how a patient will respond to different medications, allowing them to avoid ineffective or potentially harmful treatments. Furthermore, genomics can reveal individual differences in drug

metabolism, guiding personalized dosage adjustments. Genes such as those in the CYP450 enzyme family significantly influence drug metabolism, with specific variants leading to either accelerated or slowed drug processing, which in turn affects drug efficacy and safety[119]. Through genetic testing, healthcare providers can understand a patient's drug metabolism characteristics, enabling rational dosage adjustments and reducing adverse effects.

Future Directions

As genomic technologies continue to advance, they are expected to play an increasingly vital role in the diagnosis and treatment of septic shock. Ongoing clinical research will further explore the application of genomics in this field, contributing to the development of precision medicine and offering more accurate and effective treatment options for patients.

8. Prospects and Challenges

Despite advancements in septic shock management, numerous challenges persist. Early diagnosis and treatment of septic shock require the integration of vast amounts of data generated through various technological means, including imaging, genomics, hemodynamics, and pathogenetic data[83]. The effective integration and interpretation of these data necessitate advanced bioinformatics tools and specialized expertise to ensure that the information is both accurate and clinically actionable[120]. Future research should focus on developing more robust data integration platforms and analytical tools to provide timely and precise clinical decision support.

Cost and Accessibility

The application of high-tech approaches, such as genomics, artificial intelligence, and metagenomic sequencing, often comes with significant costs, which can limit their widespread use in resource-constrained healthcare settings. There is a pressing need to explore more cost-effective solutions that can extend the benefits of these technologies to a broader patient population. Future efforts should be directed toward the research and development of low-cost, efficient diagnostic and therapeutic methods, thereby promoting the broader adoption and application of these innovations.

Data Security and Ethical Considerations

The use of genomics and artificial intelligence in managing septic shock involves handling large volumes of sensitive patient data, including health and genetic information. Establishing stringent data protection protocols and ethical review mechanisms is essential to safeguard patient privacy and ensure data security, preventing potential data breaches and misuse. Additionally, securing informed patient consent and ensuring transparency in data usage are critical ethical concerns that must be addressed.

Multidisciplinary Collaboration

Effective management of septic shock requires collaboration across a multidisciplinary team, including intensivists, epidemiologists, geneticists, pharmacologists, and data scientists. Such collaboration allows for the synthesis of expertise from various fields, facilitating the development and implementation of comprehensive treatment plans. Future research and clinical practice should aim to enhance interdisciplinary communication and collaboration, fostering the utilization of multidisciplinary teams in clinical settings.

Challenges in Translating Research into Practice

While genomics and artificial intelligence offer the promise of personalized treatment, significant challenges remain in translating these findings into clinical practice. Further research is needed to validate the efficacy and safety of personalized treatment strategies, and to develop tailored treatment plans suited to different patient groups. Future studies should emphasize the exploration of individual differences, aiming to devise more precise and personalized treatment approaches to improve patient outcomes.

Clinical Validation of New Technologies

The clinical application of emerging technologies and strategies requires a rigorous validation process. Large-scale clinical trials and multicenter studies are essential for confirming the effectiveness and safety of new approaches. Future research should prioritize the design and implementation of such trials, using high-quality clinical data to validate the impact of new technologies and strategies,

ultimately promoting their integration into clinical practice.

In Conclusion

In summary, the successful treatment of septic shock demands continuous efforts in data integration, cost control, ethical safeguards, multidisciplinary collaboration, personalized treatment, and clinical validation. By incorporating various technological tools such as imaging, molecular biology, pharmacology, hemodynamics, and artificial intelligence, early precision diagnosis and individualized treatment offer new hope for improving the prognosis of septic shock patients. Overcoming these challenges in future research and practice will be crucial to driving continued progress and development in septic shock management.

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在读期间科研成果简介

一、发表论文情况

1. 第一作者：**Ngan Chansokhon**, Zeng Xueying, Lia Thongher, Yin Wanhong, **Kang Yan**. Cardiac index and heart rate as prognostic indicators for mortality in septic shock: A retrospective cohort study from the MIMIC-IV database. Heliyon,2024.e28956, (SCIE, D 级, IF 3.4, ISSN: 2405-8440)

二、参与科研课题情况

1. 2024 年亚太重症监护研讨会 Asia Pacific Intensive Care Symposium (APICS)2024 (国际：新加坡) (**E-Poster, Topic:** The Impact of Cardiac Index on Mortality in Patients with Septic Shock: A Retrospective Study from the MIMIC-IV Database),2024 August 17-19.

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