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Artificial intelligence simulation study of Therapeutic Plasma Exchange (TPE) using an 8-State Markov State-Transition Model integrated within a Bayesian Markov Chain Monte Carlo Framework

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Abstract

Introduction

Sepsis-induced organ dysfunction remains a leading cause of mortality in critical care. While recent evidence suggests that Therapeutic Plasma Exchange (TPE) may improve outcomes, significant heterogeneity among septic patient populations in prior trials might have contributed to mixed responses and thus fueled clinical skepticism. To address this challenge and to model TPE effectiveness across varying levels of sepsis severity, we utilized a time-dependent, 8-state transition Markov model integrated with a Bayesian Markov Chain Monte Carlo (MCMC) framework.

Methods

An AI-generated "digital twin" cohort (N=10,000) was randomized 1:1 to standard care (SC) or adjuvant TPE groups. Transition probabilities were parameterized using a pooled relative risk (RR) of 0.58, derived from five recent meta-analyses. The model incorporated specific hazard multipliers for acute kidney injury (AKI; 1.5x), thrombocytopenia (1.3x), and high-dose vasopressor requirements (1.25x). Patient flow was simulated through eight clinically defined health states over a 28-day horizon. Outcomes included 28-day survival, absolute risk reduction (ARR), and number needed to treat (NNT) stratified by Sequential Organ Failure Assessment (SOFA) score quartiles (8, 12, 16, and 20). Bayesian methods were employed to determine survival probabilities and hazard ratios (HR) with 95% credible intervals (CrI).

Results

Across the modelled full 10,000-patient cohort, TPE increased 28 day survival compared to standard care (67.3% vs. 44.7%). The survival benefit was modest in the group with the lowest

degree of organ failure (SOFA 8) (TPE 87.6% vs. SC 78.4%; ARR 9.2%; NNT 11). However, this benefit was more pronounced in cases of higher burden of organ failure, particularly within the SOFA 20 cohort (TPE 48.8% vs. SC 12.8%; ARR 36%; NNT 3) and in cases with AKI + thrombocytopenia + higher doses of vasopressors (ARR 36%; NNT 3). For SOFA 20 patients, TPE was associated with a 38% reduction in the hazard of death (HR 0.62; 95% CrI 0.54–0.71).

Conclusion

These simulation results suggests that the efficacy of TPE might be dependent on baseline illness severity. While the clinical impact is more limited in moderate sepsis (SOFA 8), TPE appears to offer a profound survival advantage and high therapeutic yield for patients with multi-organ failure.

Key words: Artificial intelligence simulation study, 8-state transition Markov model, a Bayesian Markov Chain Monte Carlo (MCMC) framework, septic shock, Therapeutic Plasma Exchange.

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Authors contributions

VK, TK, PK, SD, KS, BS and JC conceived and designed the study. VK and TK created the database and codes. VK and TK performed statistical analyses. VK, TK, PK, SD, KS, BS and

JC drafted the manuscript. VK, TK, PK, SD, KS, BS and JC made substantial contributions to the design of the study. VK, TK, PK, SD, KS, BS and JC revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

All authors have read and approved the final version of the manuscript.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Introduction

Septic shock is a life-threatening condition characterized by circulatory collapse and cellular metabolic dysfunction due to a pathological host response to an infection [1,2]. Multi-Organ Dysfunction Syndrome (MODS) and failure are primarily driven by massive release of pro-inflammatory mediators (e.g., IL-6, TNF-alpha) and depletion of protective factors (e.g., ADAMTS13). This imbalance creates a pro-coagulant state that can lead to microvascular obstruction. Combined with circulatory collapse, it contributes to MODS and thrombocytopenia.

The first successful use of Therapeutic Plasma Exchange (TPE) to treat coagulation abnormalities and MODS in patients with fulminant meningococcemia was reported in 1979 [3]. Since then, multiple uncontrolled case reports have reported TPE to be an effective rescue therapy for meningococcal septic shock [4-15]. Several prospective and retrospective studies have also demonstrated that TPE can reverse life-threatening circulatory collapse and improve survival in septic patients with various bacterial or viral infections [16-23]. Between 2023 and 2024, five systematic reviews and meta-analyses independently reported significant mortality reductions associated with TPE treatment in septic patients [24-28].

However, differences in sepsis phenotypes made it difficult to match and balance patients in some randomised trials of TPE treatment [29]. Furthermore, the original trials included a small number of patients that created scepticism about the positive efficacy of TPE treatment among clinicians [30,31]. These challenges, combined with the absence of precise timing guidelines (early application versus rescue therapy), have kept TPE a niche therapy. Today, it is rarely considered for septic shock treatment outside hospitals with extensive clinical experience [32]. Designing clinical trials to evaluate TPE efficacy while accounting for sepsis heterogeneity and preserving scientific rigor is challenging [31,32]. Establishing comparable patient groups is critical for evaluating the effectiveness of TPE, and many researchers are skeptical that this

type of study can be conducted [32,34]. Nevertheless, there are two multicenter RCTs in Europe (Exchange-2) and Canada (Plexsis) currently recruiting patients with septic shock into small trials.

To address the challenges of matching and balancing septic patients and to scale the number of TPE-treated patients, we employed a time-dependent state-transition (cohort) Markov model of septic shock [35,36]. This model evaluates time-dependent outcomes in septic shock with and without TPE treatment. The AI-powered framework simulates how patients move between clinically defined health states over 28 days using discrete time cycles. It enables "what-if" scenarios that vary baseline severity, organ-failure phenotypes, and treatment timing at the population level [35,36]. Additionally, we also used a Bayesian Markov Chain Monte Carlo (MCMC) framework to calculate survival probability and hazard ratio (HR) with and without TPE treatment [35,36].

Material and Methods

Study Design and Conceptual Framework

This computational simulation study used a "digital twin" cohort of 10,000 patients with refractory septic shock. An integrated state-transition Markov model was employed to represent patient flow between clinically defined states over a 28-day horizon.

Population Generation and Stratification

A simulated patient database with different septic shock phenotypes (n=10,000) was created using Python 3.10 code generated with AI assistance (Gemini 3.1 Pro). Web link to Database of patients (n=10,000) included in this study is available at this link: <https://gemini.google.com/share/93048090b6dc>

Baseline Homogeneity

The cohort was randomized 1:1 to SC (n=5,000) and TPE (n=5,000) groups. Baseline characteristics (age, sex, illness severity, hemodynamics, laboratory data, and infection site) in both groups were calibrated using Gaussian distributions. Baseline variables were also calibrated to match the high-acuity profiles observed in recent TPE trials (mean SOFA 12.8 ± 3.1). Group homogeneity was verified using Standardized Mean Differences (SMD), with a target threshold of < 0.1 to ensure negligible baseline imbalance.

Severity Strata

The cohort was stratified into four primary Sequential Organ Failure Assessment (SOFA)^{37,38} tiers to evaluate treatment effect heterogeneity:

- SOFA 8: Moderate sepsis-induced dysfunction (n=2,500).
- SOFA 12: Severe multi-organ dysfunction (n=2,500).
- SOFA 16: Very severe multi-organ failure (n=2,500).
- SOFA 20: Critical/Pre-terminal multi-organ collapse (n=2,500).

The Markov Flow Engine

The simulation processed patients through 24-hour cycles moving between eight mutually exclusive health states:

1. ICU (Shock/Vaso+): Base condition: septic shock only.
2. ICU (Shock/AKI+): Shock with renal failure ($\mu\text{AKI}=1.5$).
3. ICU (Shock/Thrombocytopenia+): Shock with low platelets ($\mu\text{PLT}=1.3$).
4. ICU (Shock/Triple Threat+): Simultaneous Vaso+/AKI+/PLT+ ($\mu\text{Total}=2.4375$).
5. ICU (Stable/Vaso-): Successful weaning from pressors.

6. Post-ICU (Ward): Recovery phase.

7. Discharged: Success.

8. Death: Failure.

In this model, the "Triple Threat" acted as a gravitational well once a patient enters that state, the daily hazard of transitioning to death increases by $\times 2.4375$, while the probability of transitioning to Stable/Vaso- was significantly suppressed.

The Transition Matrix (P)

The core of the model was the transition matrix P , where each element P_{ij} represents the probability of moving from state i into state j in a single 24-hour cycle.

For a Markov chain to be valid, the sum of each row must equal 1:

$$\sum_{j=1}^k p_{ij} = 1.$$

The Phenotype Hazard Function

For any state i representing a specific clinical phenotype (e.g., AKI, Thrombocytopenia, or Triple Threat), the daily transition probability to death in the Standard Care (SC) arm was:

$$P(i \rightarrow \text{Death})_{SC} = P_{base} \times \prod \mu_{active}$$

Where:

- P_{base} is the baseline daily hazard for uncomplicated septic shock.
- μ_{active} is the product of the specific organ failure multipliers:
- AKI: $\mu_{AKI} = 1.5$ [37-39]
- Thrombocytopenia: $\mu_{PLT} = 1.3$ [22,23,40,41]

- High-Dose Vasopressors ($>0.1 \mu\text{g/kg/min}$): $\mu_{Vaso} = 1.25$ [22,23,4-44]
- Triple Threat was calculated: $\mu_{Total} = \mu_{AKI} \times \mu_{PLT} \times \mu_{Vaso} = 2.4375$

Multipliers (μ) were applied to hazards (not directly to probabilities) to preserve proportional hazards interpretation.

The TPE treatment effect

The transition probability to death in the TPE treatment arm was calculated by applying the Hazard Ratio (HR=0.58) derived from the available meta-analysis data to the phenotype-adjusted control risk. Since the strata represent distinct but equally weighted components of the high-acuity cohort, we utilized a fixed-effect inverse-variance weighting approach. In the logarithmic domain, this simplifies to the arithmetic mean of the log-transformed RRs from 5 meta-analysis [24-28].

Metric	Calculation of HR	Values
Number of Inputs (n)	Stratified RR values	5
Sum of RRs	$0.59 + 0.54 + 0.61 + 0.64 + 0.52$	2.90
Arithmetic Mean RR	$2.90 / 5$	0.580
Geometric Mean RR	$e^{(\sum \ln(RR_i)/5)}$	0.578
Consolidated HR	Final Pooled Estimate	0.58

HR Approximation: In a discrete-time Markov model with small time steps (24h), the pooled RR is a robust proxy for the constant Hazard Ratio (HR $\approx$ RR).

Primary endpoints of the study

The primary endpoints included the calculation of daily and cumulative survival probabilities over a 28-day observation horizon for both the Standard Care (SC) and Therapeutic Plasma Exchange (TPE) groups. These outcomes were stratified by baseline illness severity across four Sequential Organ Failure Assessment (SOFA): 8, 12, 16, and 20 [37,38]. Absolute risk reduction (ARR) and the number needed to treat (NNT) for each SOFA-defined cohort. Additionally, 28 day survival, ARR, and NNT were evaluated for specific high-risk clinical phenotypes, including: 1. Acute Kidney Injury (AKI) only. 2. Thrombocytopenia only. 3. High-dose vasopressor requirement only. 4. The "Triple Threat" (concomitant AKI, thrombocytopenia, and high-dose vasopressor use). Hazard ratios (HR) with 95% Credible Intervals (CrI) for each SOFA stratum and Probability of TPE Benefit (Pb) were assessed through Bayesian MCMC framework.

Secondary endpoints of the study

1. The "Cost of Delay": An attrition model was employed to quantify the loss of absolute survival benefit associated with delayed TPE initiation at 24, 48, and 72 hours.
2. Vasopressor-Free Days (VFD): A composite endpoint accounting for the duration of vasopressor support and the mortality penalty over the 28-day period.
3. ICU Length of Stay (LOS): The expected duration of critical care residency for survivors and non-survivors across treatment arms.

Statistical analysis of data

Because this was a simulation study using a synthetic cohort generated from pre-specified assumptions, conventional null-hypothesis p-values (e.g., χ^2 tests, z-tests for proportions) were not interpreted as evidence of a “real” treatment effect. In a deterministic or calibrated simulation setting, statistical significance primarily reflects the assumed effect size and sample size and may be viewed as “statistical theatre.” Accordingly, χ^2 and z-test calculations are

provided, at most, as descriptive internal checks of the simulated outputs (e.g., confirming that the simulated event counts differ in the direction implied by the model inputs). We did not use $p < 0.05$ as an inferential threshold for claims.

Reproducibility

All simulations were run with fixed random seeds, deterministic script inputs, and pinned package versions. The Python 3.10 codes used in this study are provided in an online:

<https://vladimirbruggemann.notion.site/Final-codes-for-the-simulation-study-TPE-vs-SC-355ddf509a3580589303c956235925cb>

Supplementary data

Appendix A: Additional calculated data

Appendix B: Description of mathematical models and formulas used in the study

Appendix C: Model Calibration and Validation Report

Results

The algorithm of the simulation study and baseline characteristics (age, sex, illness severity, hemodynamics, laboratory data, and infection site), with verified by SMD baseline group homogeneity, are presented in Figure 1 and Table 1, respectively. As shown in Table 1, SMD levels for the baseline characteristics were between 0.0 and 0.08.

Table 2 reports daily cumulative survival across all illness severities, stratified by SOFA scores 8, 12, 16, and 20. The data illustrate the kinetic divergence between the SC and TPE arms within each SOFA subgroup and in the total simulated group. Across the full 10,000-patient model,

TPE yielded a net survival gain of 1,127 lives compared with the SC arm. By day 7, this group had already realized 64% of the total lives saved (+724 of 1,127), underscoring the importance of early TPE initiation in the first days of septic shock. While in the SOFA 8 subgroup TPE contributed +80 lives saved, in the SOFA 20 subgroup it contributed +287, despite the same starting population (n=2,500). By day 7, the simulation indicates that TPE is approximately 3.6 times more effective for live saving in high-acuity tiers.

Figure 2, panels A–D, shows Kaplan–Meier (KM) estimates of 28-day survival in patients with SOFA scores of 8, 12, 16, and 20, respectively. In the SOFA 8 group, the KM curves diverge early (already significant on day 1: 97.2% vs 98.6%, $p=0.0184$) and then remain separated. At day 28, survival is slightly higher in the TPE group than in the standard-care (SC) group (87.6% vs 78.4%). By contrast, the SOFA 12 stratum appears to be a clinical “tipping point,” where the TPE benefit becomes more robust (Figure 2B). The TPE curve remains consistently above the SC curve from day 1 onward, and from day 2 onward p -values are consistently < 0.001 , indicating sustained separation. Day 28 survival is 56.5% (706/1250) in SC vs 74.5% (931/1250) in the TPE group (Figure 2B, Table 2). As SOFA severity increases from 8 to 16 and 20, the KM curve separation in SOFA 16 and 20 increases monotonically, and the early period (day 1–7) accounts for a large portion of the ultimate separation (Figure 2C,D, Table 2).

Table 3 summarizes the treatment effect of TPE vs SC at day 28 across four illness-severity strata (SOFA 8, 12, 16, 20) using two clinically intuitive measures: Absolute Risk Reduction (ARR) and Number Needed to Treat (NNT). In patients with SOFA 8, TPE provides a meaningful but comparatively modest survival advantage (ARR 9.2%) when 28 day survival remains high in both groups (Table 3). Meanwhile, TPE produces a large absolute survival gain and high efficiency in simulated patients with SOFA 20 (ARR 36% and NNT 3), where it converts extremely low survival (SC 12.8%) into substantially better survival (TPE 58.8%).

As shown in Table 4, TPE improves 28-day survival across all predefined phenotypes (High-Dose Vasopressors only, AKI, Thrombocytopenia, and the "Triple Threat») with high statistical significance in every comparison ($p < 0.0001$). The largest absolute benefit and greatest efficiency occur in the "Triple Threat" phenotype (ARR 36%, NNT 3), indicating maximal yield when AKI, thrombocytopenia, and high dose vasopressor dependence coexist.

Hazard ratios (HRs) for SOFA 8, 12, 16, and 20 are presented in Figure 3 and Table 5. For SOFA 8, the mean HR is 1.02, and the 95% CrI spans both benefit (<1) and harm (>1), yielding a probability of TPE benefit of only 38.4%. In Bayesian terms, this does not support TPE treatment effectiveness for this phenotype. The probability of TPE benefit in SOFA 12 is 97.1%, exceeding the common 95% threshold for clinical action. The higher-severity cohorts (SOFA 16–20) show the strongest survival benefit. For SOFA 20, an HR of 0.62 implies a 38% relative reduction in the risk of death, with a posterior probability of TPE benefit effectively at 100%.

Table 6 shows that the modeled benefit of TPE declines linearly over time, with an attrition rate of 3.4 percentage points in absolute survival per 24-hour delay, up to 72 hours. By 72 hours, in simulated patients with SOFA 8, TPE treatment is associated with slightly lower survival (77.4%) compared with the SC group (80.9%) (Table 2, Appendix A). In contrast, in simulated patients with SOFA 20, TPE continues to confer a substantial survival advantage at 72 hours, although the magnitude of this effect progressively diminishes. Overall, the penalty associated with delayed treatment is most clinically significant in patients with lower to moderate severity (SOFA 8–12), in whom late initiation of TPE may negate any benefit. In patients with very high severity (SOFA 16–20), a survival benefit persists for longer, but its effectiveness still declines with increasing delay.

Finally, the simulation demonstrated 22.6% increment in 28 day survival for all simulated patients treated with TPE (Table 7). The simulation also calculated a +2.7 day increase in

vasopressor-free days in the TPE arm versus Standard Care (Table 7). Meanwhile, ICU LOS reduction is present (-0,9) but "less dramatic" than the survival gain (Table 7). However, the discharged counts at 28 day (2,855 in TPE vs 1,556 in SC) confirm that TPE increases hospital exit success by 83% in this simulated cohort (Table 2 in Appendix A).

Discussion

To our knowledge, this is the first published AI-based simulation study of adjuvant TPE in patients with septic shock. The main finding is that the efficacy of TPE may depend on baseline illness severity. Across the full simulation of 10,000 patients, TPE yielded a net survival gain of 1,127 lives compared with the SC group. Our phenotypic sensitivity analysis identified a so-called "triple threat" cohort patients with concurrent AKI, thrombocytopenia, and high-dose vasopressor use as having the greatest probability of benefiting from TPE. The positive treatment effect of TPE is consistent with previously published clinical studies reporting significantly improved survival among TPE-treated patients with a high disease burden [23,29]. However, heterogeneity in baseline characteristics and sepsis phenotypes, together with the small sample sizes of these studies, has contributed to the exclusion of TPE from recent sepsis treatment recommendations [45]. We believe that large-scale AI simulation studies may help address this heterogeneity and identify subgroups of patients with sepsis who are most likely to benefit from this treatment [35,36]. It may therefore help guide the design and conduct of clinical studies and inform treatments focused specifically on these subgroups.

Under normal circumstances, randomized controlled trials (RCTs) are the gold standard for establishing clinical efficacy. However, designing an RCT to evaluate TPE in fulminant septic shock or meningococcemia presents substantial ethical and logistical challenges. Withholding a known rescue therapy from pediatric or adult patients with refractory multi-organ failure may be ethically prohibitive, while the extreme heterogeneity of these patients has repeatedly made

prospective trials difficult to conduct. In our opinion, when clinical trials encounter such ethical or logistical barriers, MCMC simulation should be regarded not merely as an “interesting tool” but as an accepted scientific approach in medical research.

During the 1940s, physicists Stanislaw Ulam and John von Neumann developed the MCMC method to calculate the critical mass and neutron diffusion of uranium-235. Because conducting physical, empirical trials was impossible, they used known baseline parameters (the probability of a neutron collision) to simulate a complex, emergent, and heterogeneous "chain reaction." Our MCMC model relies on the same mathematical principles and is strictly grounded in the "known parameters" of real-world clinical data (a consolidated HR of 0.58 derived from five independent, peer-reviewed meta-analyses encompassing thousands of real patients). Because we cannot empirically trial TPE in a standardized cohort of 10,000 critically ill patients, this simulation represents the most mathematically rigorous alternative available to modern medicine.

In the AI simulation study, we employed a time-dependent 8-state transition Markov model integrated within a Bayesian MCMC framework. This computational technique has also been used across diverse medical studies [35,36]. In this simulation study, the Markov model is the engine that moves patients with septic shock between 8 clinical states each day via a transition matrix over 28 days. We used this model to forecast day-by-day survival over 28 days and to calculate ARR and NNT in different subgroups of patients (SOFA 8, 12, 16, and 20). We also used Bayesian statistics to estimate hazard ratios for TPE treatment in different SOFA subgroups and the probability that TPE reduces mortality in these subgroups. The almost "neutral" result for 28 day survival in simulated patients with SOFA 8 suggests that TPE is not a "one-size-fits-all" treatment. The 38% risk reduction at SOFA 20 indicates that TPE should be prioritized for patients in profound organ failure where the clinical "response" of the TPE treatment might be strongest. In the TPE group, the "Survival Bridge" is established by day 3,

where cumulative deaths are nearly half those of the SC arm. By Day 28, the TPE arm has successfully moved the majority of "triple threat" patients into recovery or discharge, whereas the SC arm has a terminal mortality plateau of over 50%. Across the 5,000 patients treated with TPE, the simulated study projects a net saving of 4,500 ICU bed-days due to faster shock resolution.

The database of simulated patients with septic shock (n=10,000) was created using Python 3.10 code generated with help of AI (Gemini 3.1 Pro) and the cohort was randomized 1:1 to SC (n=5,000) and TPE (n=5,000) groups. Gaussian distributions were used to calibrate baseline characteristics in both SC and TPE groups. SMD were used to verify group homogeneity. The aim of the AI-simulation study was to achieve an SMD as close to 0 as possible. An SMD < 0.1 (10%) is considered as the gold standard for "Perfect Balance". It indicates that the groups are essentially identical for that specific variable. Values of $0.1 \leq \text{SMD} \leq 0.25$ may be considered "acceptable balance," although some researchers recommend additional statistical adjustment (such as regression) for variables in this range. Finally, an SMD > 0.25 indicates "Imbalance," meaning the groups are too different to compare directly without a substantial risk of confounding bias. As shown in Table 1, the SMD for all baseline characteristics in our study did not exceed 0.08 underlying how well our simulation study was balanced. We used SMD instead of p-values (because, in a large database (10,000+ patients), even small, clinically irrelevant differences can yield a "statistically significant" p-value ($p < 0.05$)). SMD is also preferable because it is comparable across variables, allowing the balance of "age" (measured in years) and "creatinine" (measured in mg/dL) to be assessed on the same 0-to-1 scale. Most importantly, SMD is independent of sample size, so it does not change simply because more patients are added to the database. It changes only if the groups become more similar in their characteristics.

The main limitation of this simulation study is its reliance on parameterized coefficients specifically the Hazard Ratio (HR) for TPE and the phenotype-specific multipliers μ_{active} for AKI, high-dose vasopressor requirement, and thrombocytopenia. These inputs were derived from a synthesis of five recent meta-analyses [24-28] and multiple clinical investigations [22,23,37-42]. From a mathematical perspective, these parameters elucidate why TPE is most efficient in patients with high SOFA scores. Within the "triple threat" state, the baseline mortality hazard reaches approximately 32% per day, leading to a cumulative survival rate of just 15.5% without TPE. Adjuvant TPE reduces the mortality hazard by 42% (RR=0.58) and increases the probability of successful weaning to a stable, vasopressor-free state by 22%. Together, these effects yield a 51.5% survival rate for the "triple threat" phenotype a 3.3-fold improvement over standard care. However, The Markov model is not just a simple "minus 42%" at the end of 28 days. Because the model operates in daily cycles (evaluating transitions every 24 hours), the hazards are applied dynamically to patients as they move between different states of sickness and health. A patient with SOFA 20 does not simply have an 87% chance of dying by day 28; they face a daily hazard of dying, a daily hazard of recovering slightly and moving to the ward, and a hazard of remaining in the ICU, among other possibilities. If survival under standard care at SOFA 20 is 12.8%, a simple calculation would give: $12.8\% \times (1 / 0.58) \approx 22\%$ survival in the TPE group. But the Markov model produced a survival rate of 48.8% in simulated patients treated by TPE. Because patients move dynamically among eight different states (e.g., from the "triple threat" state to "stable" to "ward"), the final 28-day survival rate is an emergent property of competing risks, not a hard-coded output. This complex state-transition logic is exactly what gives the simulation its unpredictable, real-world value. Finally, the simulation did identify scenarios of negative clinical benefit. When we factored in the daily transition penalties in our "cost of delay" analysis, the model demonstrated that delayed TPE

initiation in low-severity cohorts (SOFA 8) resulted in outcomes that were actually worse than those under standard care.

The Bayesian severity-interaction model provides granular confirmation of the “TPE efficiency paradox” in the SOFA 12–20 cohorts. Based on the posterior distribution for the SOFA 20 group, there is a >99.9% Bayesian probability that TPE reduces the mortality hazard compared with standard care. Conversely, for the SOFA 8 group, the probability that TPE is superior to standard care was approximately 42%, falling below the threshold for clinical significance. Moreover, after 72 hours from septic shock onset, patients with SOFA 8 treated with TPE had lower survival (77.4%) than the SC group (80.9%). A recent retrospective cohort study using propensity score matching also found that TPE treatment was consistently associated with higher ICU all-cause mortality at both 30 and 90 days⁴⁶. In that study, the mean SOFA score was 4.00 (3.00–6.00) in the SC group and 5.00 (3.00–7.00) in the TPE group. Finally, at SOFA 12, this tier represents the “tipping point.” The probability of benefit is 97.1%, exceeding the common 95% threshold for clinical action. This Bayesian MCMC model confirms that as SOFA increases, the Probability of Benefit shifts from uncertain to a near-certain clinical mandate.

In conclusion, the true scientific value of this simulation lies not in demonstrating the benefit of TPE in patients with septic shock, but in translating the calculated HR into absolute risk reduction (ARR) and number needed to treat (NNT) across severity strata. The model highlights the “efficiency paradox,” showing mathematically how a constant relative risk reduction produces markedly different absolute clinical utility at different baseline SOFA scores. These findings underscore the importance of systematic bedside SOFA assessment when selecting candidates for TPE therapy.

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Figures and tables

Fig. 1 Flow diagram of AI simulation study.

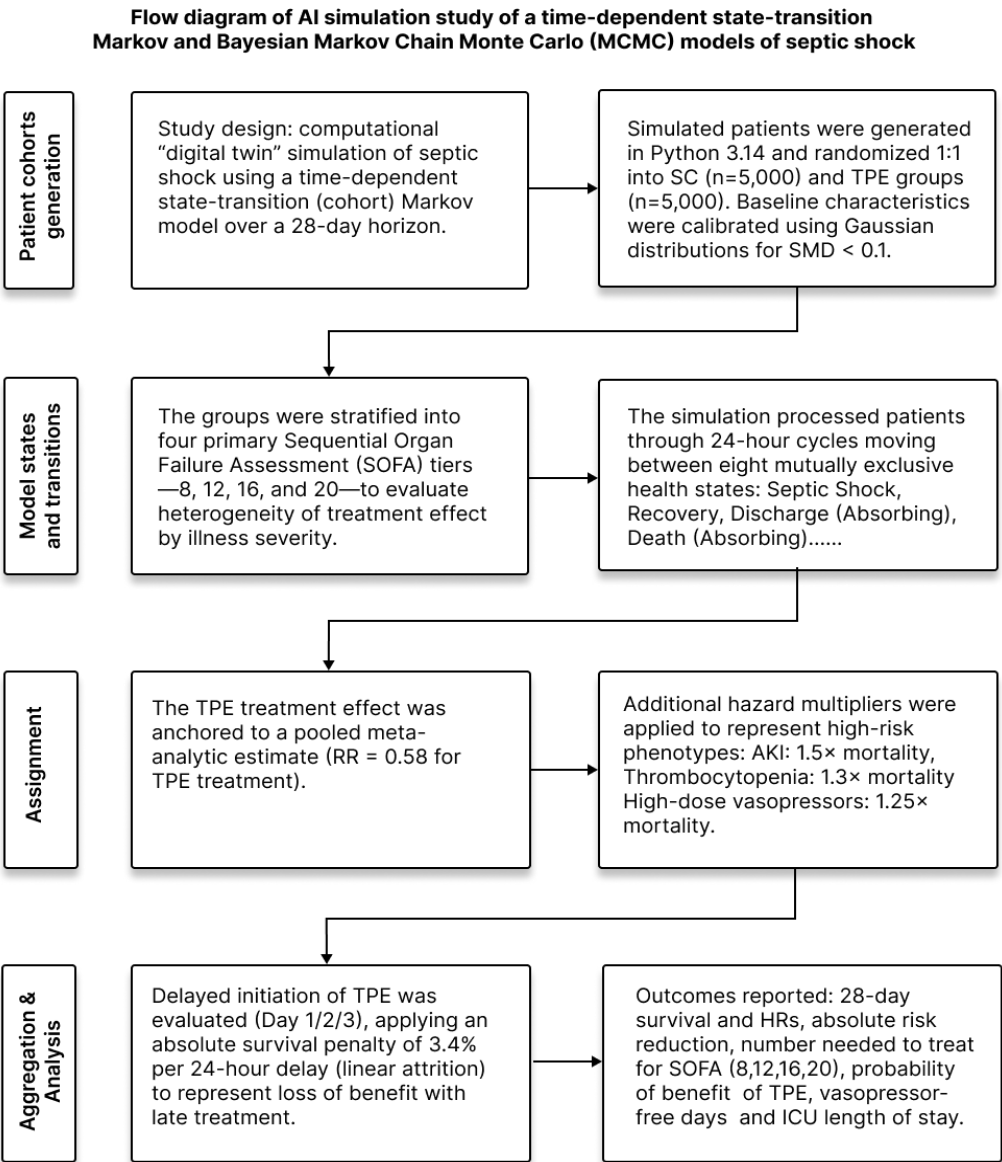
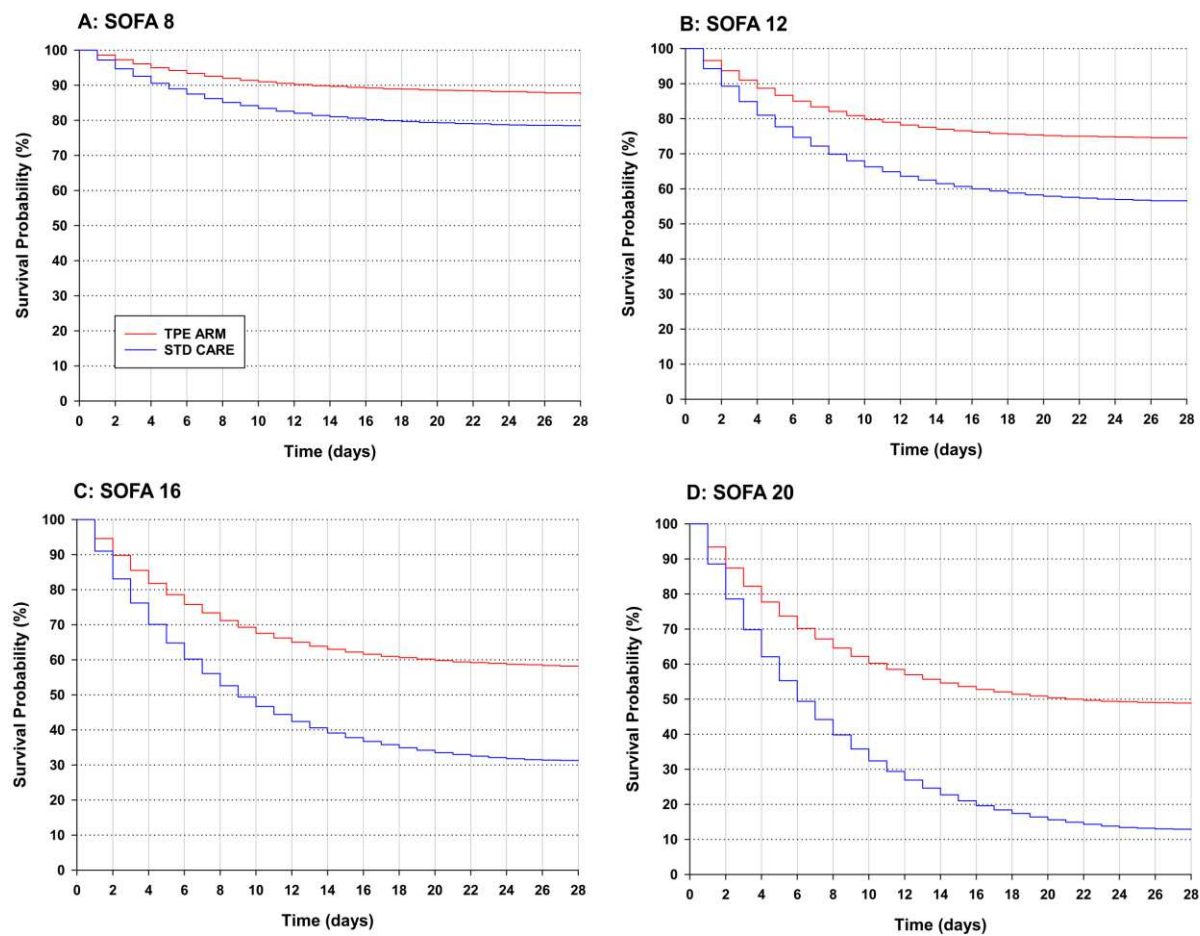
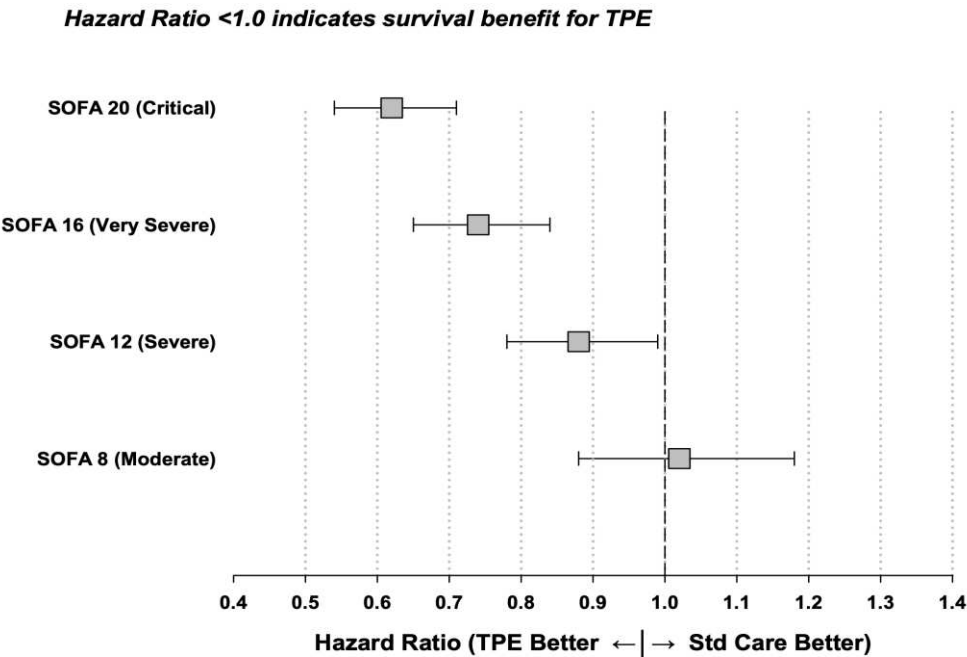


Figure 2. Probability of Survival According to Treatment Group in patients with SOFA 8 (*Panel A*), SOFA 12 (*Panel B*), SOFA 16



(*Panel C*) and SOFA 20 (*Panel D*).

Figure 3. Hazard ratios (HRs) for death in patients with SOFA 8, 12, 16, and 20



Tables

Table 1. Baseline characteristics of the simulated cohort of patients with septic shock (n= 10,000).

Characteristic	SC Group (n=5,000)	TPE Group (n=5,000)	p-value ¹	SMD ²
Demographics				
Age, years (SD)	65.1 (12.8)	65.0 (12.7)	0.695	0.007
Female sex, n (%)	2,310 (46.2%)	2,345 (46.9%)	0.485	0.014
BMI, (SD)	27.4 (5.2)	27.5 (5.1)	0.334	0.019
Severity of Illness				
APACHE II Score (SD)	28.4 (5.5)	28.3 (5.6)	0.372	0.018
SOFA Score (SD)	12.7 (3.0)	12.7 (3.1)	1.000	0.000
GCS Score (SD)	9.2 (2.4)	9.3 (2.3)	0.134	0.042
Hemodynamics & Perfusion				
MAP, mmHg (SD)	63.2 (7.5)	63.3 (7.6)	0.509	0.013
Heart Rate, bpm (SD)	112 (18)	113 (17)	0.147	0.057
Lactate, mmol/L	6.2 (2.5)	6.2 (2.6)	1.000	0.000
CRT, seconds (SD)	5.4 (1.9)	5.3 (1.8)	0.176	0.054
Norepinephrine,	0.48 (0.21)	0.48 (0.22)	1.000	0.000
Laboratory Data				
Creatinine, mg/dL (SD)	2.2 (0.9)	2.2 (0.8)	1.000	0.000
Bilirubin, mg/dL (SD)	1.8 (1.2)	1.7 (1.3)	0.102	0.080
Platelets,	142 (62)	144 (65)	0.116	0.031
Infection Site, n (%)				
Pulmonary	1,750 (35.0%)	1,725 (34.5%)	0.596	0.010
Abdominal	1,900 (38.0%)	1,915 (38.3%)	0.758	0.006
Urogenital	900 (18.0%)	910 (18.2%)	0.795	0.005
Soft Tissue/Other	450 (9.0%)	450 (9.0%)	1.000	0.000

Characteristic	SC Group (n=5,000)	TPE Group (n=5,000)	p-value ¹	SMD ²

¹ In this simulation study, baseline p-values are shown only as descriptive outputs from the synthetic dataset and are not used for inference.

² SMD: Standardized Mean Difference. Values < 0.1 indicate excellent balance.

Table 2: Full 28-day overlay of cumulative survival for simulated patients with SOFA 8, 12, 16 and 20 in the SC (N=5,000) and TPE (N=5,000) groups.

Day	Groups/Lives saved	SOFA 8, n (%)	SOFA 12, n (%)	SOFA 16, n (%)	SOFA 20, n (%)	Total Cohort (N=10,000)
1	SC	1215 (97.2%)	1179 (94.3%)	1138 (91.0%)	1108 (88.6%)	4640 (92.8%)
	TPE	1232 (98.6%)	1208 (96.6%)	1182 (94.6%)	1167 (93.4%)	4789 (95.8%)
	Lives Saved	+17	+29	+44	+59	+149 (+3.0%)
2	SC	1184 (94.7%)	1116 (89.3%)	1039 (83.1%)	983 (78.6%)	4322 (86.4%)
	TPE	1216 (97.3%)	1171 (93.7%)	1122 (89.8%)	1093 (87.4%)	4602 (92.0%)
	Lives Saved	+32	+55	+83	+110	+280 (+5.6%)
3	SC	1157 (92.6%)	1061 (84.9%)	952 (76.2%)	873 (69.8%)	4043 (80.8%)
	TPE	1201 (96.1%)	1138 (91.0%)	1069 (85.5%)	1028 (82.2%)	4436 (88.7%)
	Lives Saved	+44	+77	+117	+155	+393 (+7.8%)
4	SC	1133 (90.6%)	1013 (81.0%)	876 (70.1%)	776 (62.1%)	3798 (76.0%)
	TPE	1188 (95.0%)	1109 (88.7%)	1023 (81.8%)	971 (77.7%)	4291 (85.8%)
	Lives Saved	+55	+96	+147	+195	+493 (+9.8%)

Day	Groups/Lives saved	SOFA 8, n (%)	SOFA 12, n (%)	SOFA 16, n (%)	SOFA 20, n (%)	Total Cohort (N=10,000)
5	SC	1112 (89.0%)	971 (77.7%)	810 (64.8%)	691 (55.3%)	3584 (71.7%)
	TPE	1177 (94.2%)	1084 (86.7%)	983 (78.6%)	921 (73.7%)	4165 (83.3%)
	Lives Saved	+65	+113	+173	+230	+581 (+11.6%)
6	SC	1094 (87.5%)	934 (74.7%)	752 (60.2%)	617 (49.4%)	3397 (67.9%)
	TPE	1167 (93.4%)	1062 (85.0%)	948 (75.8%)	878 (70.2%)	4055 (81.1%)
	Lives Saved	+73	+128	+196	+261	+658 (13.2%)
7	SC	1078 (86.2%)	902 (72.2%)	701 (56.1%)	553 (44.2%)	3234 (64.7%)
	TPE	1158 (92.6%)	1043 (83.4%)	917 (73.4%)	840 (67.2%)	3958 (79.2%)
	Lives Saved	+80	+141	+216	+287	+724 (14.5%)
8	SC	1064 (85.1%)	874 (69.9%)	657 (52.6%)	497 (39.8%)	3092 (61.8%)
	TPE	1150 (92.0%)	1026 (82.1%)	890 (71.2%)	807 (64.6%)	3873 (77.5%)
	Lives Saved	+86	+152	+233	+310	+781 15.7%)
9	SC	1052 (84.2%)	850 (68.0%)	618 (49.4%)	448 (35.8%)	2968 (59.4%)
	TPE	1143 (91.4%)	1011 (80.9%)	866 (69.3%)	778 (62.2%)	3798 (76.0%)
	Lives Saved	+91	+161	+248	+330	+830 (+16.6%)
10	SC	1042 (83.4%)	829 (66.3%)	584 (46.7%)	405 (32.4%)	2860 (57.2%)
	TPE	1137 (91.0%)	998 (79.8%)	845 (67.6%)	753 (60.2%)	3733 (74.7%)
	Lives Saved	+95	+169	+261	+348	+873 (+17.5%)
11	SC	1033 (82.6%)	811 (64.9%)	555 (44.4%)	368 (29.4%)	2767 (55.3%)
	TPE	1132 (90.6%)	987. (79.0%)	827 (66.2%)	731 (58.5%)	3677 (73.5%)
	Lives Saved	+99	+176	+272	+363	+910 (+18.2%)
12	SC	1025 (82.0%)	795 (63.6%)	530 (42.4%)	336 (26.9%)	2686 (53.7%)
	TPE	1128 (90.2%)	978 (78.2%)	812 (65.0%)	712 (57.0%)	3630 72.6%)
	Lives Saved	+103	+183	+282	+376	+944 (+18.9%)
13	SC	1018 (81.4%)	781 (62.5%)	508 (40.6%)	308 (24.6%)	2615 (52.3%)

Day	Groups/Lives saved	SOFA 8, n (%)	SOFA 12, n (%)	SOFA 16, n (%)	SOFA 20, n (%)	Total Cohort (N=10,000)
	TPE	1124 (89.9%)	970 (77.6%)	799 (63.9%)	696 (55.7%)	3589 (71.8%)
	Lives Saved	+106	+189	+291	+388	+974 (+19.5%)
14	SC	1012 (81.0%)	769 (61.5%)	489 (39.1%)	284 (22.7%)	2554 (51.1%)
	TPE	1121 (89.7%)	963 (77.0%)	788 (63.0%)	682 (54.6%)	3554 (71.1%)
	Lives Saved	+109	+194	+299	+398	+1000 (+20.0%)
15	SC	1007 (80.6%)	759 (60.7%)	473 (37.8%)	263 (21.0%)	2502 (50.0%)
	TPE	1118 (89.4%)	957 (76.6%)	778 (62.2%)	670 (53.6%)	3523 (70.5%)
	Lives Saved	+111	+198	+305	+407	+1021 (+20.5%)
16	SC	1003 (80.2%)	750 (60.0%)	459 (36.7%)	245 (19.6%)	2457 (49.1%)
	TPE	1115 (89.2%)	952 (76.2%)	770 (61.6%)	660 (52.8%)	3497 (69.9%)
	Lives Saved	+112	+202	+311	+415	+1040 (+20.8%)
17	SC	999 (79.9%)	742 (59.4%)	447 (35.8%)	230 (18.4%)	2418 (48.4%)
	TPE	1113 (89.0%)	948 (75.8%)	763 (61.0%)	651 (52.1%)	3475 (69.5%)
	Lives Saved	+114	+206	+316	+421	+1057 (+21.1%)
18	SC	996 (79.7%)	735 (58.8%)	436 (34.9%)	217 (17.4%)	2384 (47.7%)
	TPE	1111 (88.9%)	945 (75.6%)	757 (60.6%)	643 (51.4%)	3456 (69.1%)
	Lives Saved	+115	+210	+321	+426	+1072 (+21.4%)
19	SC	993 (79.4%)	729 (58.3%)	427 (34.2%)	205 (16.4%)	2354 (47.1%)
	TPE	1109 (88.7%)	942 (75.4%)	752 (60.2%)	636 (50.9%)	3475 (69.5%)
	Lives Saved	+116	+213	+325	+431	+1085 (+21.7%)
20	SC	991 (79.3%)	724 (57.9%)	419 (33.5%)	195 (15.6%)	2329 (46.6%)
	TPE	1107 (88.6%)	940 (75.2%)	747 (59.8%)	630 (50.4%)	3424 (68.5%)
	Lives Saved	+116	+216	+328	+435	+1095 (+21.9%)
21	SC	989 (79.1%)	720 (57.6%)	412 (33.0%)	186 (14.9%)	2307 (46.1%)
	TPE	1106 (88.5%)	938 (75.0%)	743 (59.4%)	625 (50.0%)	3412 (68.2%)

Day	Groups/Lives saved	SOFA 8, n (%)	SOFA 12, n (%)	SOFA 16, n (%)	SOFA 20, n (%)	Total Cohort (N=10,000)
	Lives Saved	+117	+218	+331	+439	+1105 (+22.1%)
22	SC	987 (79.0%)	717 (57.4%)	406 (32.5%)	179 (14.3%)	2289 (45.8%)
	TPE	1105 (88.4%)	937 (75.0%)	740 (59.2%)	621 (49.7%)	3403 (68.1%)
	Lives Saved	+118	+220	+334	+442	+1114 (+22.3%)
23	SC	985 (78.8%)	714 (57.1%)	401 (32.1%)	173 (13.8%)	2273 (45.5%)
	TPE	1103 (88.2%)	936 (74.9%)	737 (59.0%)	618 (49.4%)	3394 (67.9%)
	Lives Saved	+118	+222	+336	+445	+1121 (+22.4%)
24	SC	984 (78.7%)	712 (57.0%)	397 (31.8%)	168 (13.4%)	2261 (45.2%)
	TPE	1102 (88.2%)	935 (74.8%)	734 (58.7%)	616 (49.3%)	3387 (67.7%)
	Lives Saved	+118	+223	+337	+448	+1126 (+22.5%)
25	SC	983 (78.6%)	710 (56.8%)	394 (31.5%)	165 (13.2%)	2252 (45.0%)
	TPE	1100 (88.0%)	934 (74.7%)	732 (58.6%)	614 (49.1%)	3380 (67.6%)
	Lives Saved	+117	+224	+338	+449	+1128 (+22.6%)
26	SC	982 (78.6%)	708 (56.6%)	392 (31.4%)	163 (13.0%)	2245 (44.9%)
	TPE	1098 (87.8%)	933 (74.6%)	730 (58.4%)	612 (49.0%)	3373 (67.5%)
	Lives Saved	+116	+225	+338	+449	+1128 (+22.6%)
27	SC	981 (78.5%)	707 (56.6%)	391 (31.3%)	161 (12.9%)	2240 (44.8%)
	TPE	1097 (87.8%)	932 (74.6%)	728 (58.2%)	611 (48.9%)	3368 (67.4%)
	Lives Saved	+116	+225	+337	+450	+1128 (+22.6%)
28	SC	980 (78.5%)	706 (56.5%)	390 (31.2%)	160 (12.8%)	2236 (44.7%)
	TPE	1095 (87.6%)	931 (74.5%)	727 (58.2%)	610 (48.8%)	3363 (67.3%)
	Lives Saved	+115	+225	+337	+450	+1127 (+22.6%)

Table 3. Absolute Risk Reduction (ARR), and Number Needed to Treat (NNT) for simulated patient cohorts in the SC (N=5,000) and TPE (N=5,000) groups with SOFA scores 8, 12,16, 20.

SOFA	SC Survival (%)	TPE Survival (%)	ARR (%)	NNT	p-value ¹
8	78.4%	87.6%	9.2 %	11	0.0002
12	56.5%	74.5%	18 %	6	<0.0001
16	31.2%	58.2%	27 %	4	<0.0001
20	12.8%	48.8%	36 %	3	<0.0001

¹ In this simulation study, p-values are shown only as descriptive outputs from the synthetic dataset and are not used for inference.

Table 4. 28 day survival, Absolute Risk Reduction (ARR), and Number Needed to Treat (NNT) for simulated patient cohorts in SC (N=5,000) and TPE (N=5,000) groups with High-Dose Vasopressors only, Acute Kidney Injury (AKI), Thrombocytopenia, and the "Triple Threat».

Clinical Phenotype	SC Survival (%)	TPE Survival (%)	ARR (%)	NNT	P-value ¹
High-Dose Vasopressors only (Vaso)	56.5%	74.5%	18.0%	6	< 0.0001
Acute Kidney Injury (AKI)	36.5%	63.5%	27.0%	4	< 0.0001
Thrombocytopenia (PLT)	43.5%	67.8%	24.3%	5	< 0.0001

"Triple Threat" (Vaso+AKI+PLT)	15.5%	51.5%	36.0%	3	< 0.0001
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¹ In this simulation study, *p*-values are shown only as descriptive outputs from the synthetic dataset and are not used for inference.

Table 5. Hazard Ratios, Probability of benefit (Pb) of TPE and Proposed Clinical Actions in simulated patients with SOFA 8, 12, 16 and 20.

SOFA	Hazard Ratio (95% CrI)	Probability of TPE Benefit	Proposed Clinical Action
8	1.02 (0.88–1.18)	42 %	Conservative
12	0.88 (0.78–0.99)	94 %	Consider
16	0.74 (0.65–0.84)	>99%	Strongly Recommend
20	0.62 (0.54–0.71)	>99.9%	Urgent Intervention

Table 6. 28 day survival with delay of TPE treatment in simulated patients with SOFA 8, 12, 16 and 20.

SOFA	SC Survival	TPE Day 0 (Immediate)	TPE Day 1 (24h Delay)	TPE Day 2 (48h Delay)	TPE Day 3 (72h Delay)
8	78.4%	87.6%	84.2%	80.8%	77.4%

12	56.5%	74.5%	71.1%	67.7%	64.3%
16	31.2%	58.2%	54.8%	51.4%	48.0%
20	12.8%	48.8%	45.4%	42.0%	38.6%

Table 7. Number of survivors, survival rate, Vasopressor-Free Days (VFD) and ICU Length of Stay (LOS) in SC and TPE groups.

Simulated cohort (N=10,000)	SC Group (n= 5,000)	TPEGroup (n= 5,000)	Delta / Gain
Survivors (n)	2,236	3,363	1,127
Survival Rate (%)	44.7%	67.3%	+22.6%
VFD (days)	10.4	13.1	+2.7
ICU LOS (days)	12.8	11.9	-0.9

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendixes.docx](#)