

Adjunctive Atorvastatin for Sepsis in the Acute Medical Unit: A Randomized Controlled Trial

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Abstract

Background: Sepsis, a devastating syndrome of organ dysfunction triggered by a dysregulated host response to infection, remains a leading cause of global mortality. Statins, renowned for lipid-lowering, also exhibit potent anti-inflammatory and endothelial-stabilizing properties, offering a theoretical advantage in the septic milieu. This study investigated whether adjunctive atorvastatin could improve survival and modulate key sepsis-related outcomes.

Methods: In this open-label, randomized controlled trial conducted in the acute medical unit of a tertiary academic center, adult patients with sepsis (defined as suspected infection plus a SOFA score increment of ≥ 2) were allocated to receive either standard sepsis management plus daily oral atorvastatin 20mg or standard management alone for up to 28 days. The primary endpoint was 28-day all-cause mortality. Secondary endpoints included requirements for organ support, duration of hospitalization, and kinetic changes in C-reactive protein (CRP), procalcitonin (PCT), and lactate. Analysis adhered to intention-to-treat principles.

Results: Sixty-eight patients were randomized (36 atorvastatin, 32 control). While 28-day mortality trended lower in the atorvastatin arm (36% vs. 56% in controls; Risk Difference -20%, 95% CI -45% to 5%), this difference did not achieve statistical significance ($p=0.10$). Similarly, no significant benefits were observed in organ support needs or hospital stay. Critically, atorvastatin administration led to a significant and more pronounced reduction in both procalcitonin (median change -8 vs 0 ng/ml, $p=0.005$) and lactate levels (median change -0.95 vs -0.62 mmol/l, $p=0.048$) by day 7.

Conclusion: While adjunctive atorvastatin did not demonstrably reduce 28-day mortality in this sepsis cohort, its significant impact on attenuating procalcitonin and lactate levels suggests a beneficial modulation of underlying inflammatory and metabolic derangements.

Keywords

Sepsis, Statins, Atorvastatin, Mortality, Randomized Controlled Trial, Inflammation, Procalcitonin, Lactate, Emergency Medicine

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Introduction

Sepsis, a syndrome characterized by life-threatening organ dysfunction stemming from a dysregulated host immunological response to infection, constitutes a formidable global health challenge, exacting a significant toll in terms of morbidity and mortality.^{1,2} The pathophysiological cascade of sepsis is characterized by an intricate interplay of exuberant pro-inflammatory cascades, counter-regulatory anti-inflammatory processes, profound endothelial dysfunction, and widespread coagulopathy, culminating in microcirculatory collapse, pervasive tissue hypoxia, and the evolution of multi-organ dysfunction syndrome (MODS).³

HMG-CoA reductase inhibitors, or statins, are ubiquitously prescribed for their established lipid-lowering efficacy. However, accumulating evidence underscores their capacity to exert a spectrum of pleiotropic effects, distinct from their impact on cholesterol homeostasis. These encompass potent immunomodulatory actions, inherent antioxidant

properties and amelioration of endothelial dysfunction.⁴ Such non-lipid-mediated attributes postulate a potential therapeutic utility for statins in diverse clinical states hallmarked by systemic inflammation, prominently including sepsis.⁵ Indeed, preclinical investigations and several observational human studies have intimated an association between statin utilization and a diminished incidence of sepsis, attenuated disease severity, and more favorable clinical trajectories, including reduced mortality.⁶⁻¹¹ Notwithstanding these promising signals, evidence from randomized controlled trials (RCTs) has yielded divergent findings, with some studies failing to corroborate these benefits and, in certain contexts, suggesting neutral or even potentially deleterious effects, particularly with acute, high-dose regimens or within specific septic patient cohorts.¹²⁻¹⁵

Against this backdrop of clinical equipoise and the unremittingly high mortality associated with sepsis, the imperative for rigorously designed RCTs remains.^{16,17} The present investigation was, therefore,

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conceived to critically appraise the therapeutic efficacy of adjunctive atorvastatin in diminishing 28-day mortality and ameliorating other salient clinical and biochemical parameters in adult patients presenting with sepsis to an acute medical emergency setting.

Methods

2.1. Trial Design and Ethical Oversight

This investigator-led, open-label, parallel-group, randomized controlled trial was conducted within the acute medical admissions unit of Nehru Hospital, a constituent of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India—a prominent tertiary care academic medical center. The study protocol received approval from the Institutional Ethics Committee of PGIMER, Chandigarh (Ref: INT/IEC/2023/SPL-1137). The trial was prospectively registered with the Clinical Trials Registry – India (CTRI/2024/01/061069).

2.2. Participant Selection

All screening and enrolment procedures took place in the acute medical unit. Adult patients (aged ≥ 18 years) presenting to the emergency department and subsequently admitted to the acute medical unit manifesting clinical features consistent with sepsis were considered for enrolment. Sepsis was operationalized as the presence of suspected or microbiologically confirmed infection in conjunction with acute organ dysfunction, quantified by an acute increase in Sequential Organ Failure Assessment (SOFA) score of ≥ 2 points over pre-illness baseline, assigned at acute medical unit admission immediately after emergency department triage in accordance with Sepsis-3 guidelines.¹⁸ The baseline SOFA was determined by clinical history and available records, with pre-existing chronic organ dysfunction subtracted to isolate the acute increment, per Sepsis-3 construct. For patients without known pre-existing organ dysfunction, a baseline SOFA score of zero was assumed. Patients were excluded from the study if they were pregnant, had pre-existing cardiovascular conditions requiring chronic statin therapy, active cancer, or established liver insufficiency – including decompensated cirrhosis, acute liver failure, or baseline transaminase levels exceeding five times the upper limit of normal. Exclusion also applied to individuals with known myopathic disorders or elevated baseline creatine phosphokinase (CPK) levels above 500 U/L, and those admitted due to trauma or patients requiring immediate surgical admission for primary operative source control. Prior to any trial-specific interventions or data collection, voluntary, written informed consent was obtained from each participant or their legally authorized representative.

2.3. Randomization, Allocation, and Interventions

Eligible participants who provided informed consent were randomly assigned, in a 1:1 ratio, to either the intervention or control arm, utilizing a pre-defined, computer-generated randomization sequence. Given the inherent difficulty in blinding an active oral medication against no placebo in an emergency setting with resource constraints, an open-label design was adopted, rendering both participants and investigators cognizant of treatment allocation.

- **Intervention Arm:** Participants received standard sepsis management supplemented with oral atorvastatin 20mg administered once daily.¹⁹ For patients unable to swallow tablets, the medication was crushed, suspended in water, and administered via an oro-/nasogastric tube. Atorvastatin was commenced promptly post-randomization and continued for a maximum of 28 days.

- **Control Arm:** Participants received standard sepsis management exclusively.

Concomitant standard sepsis management, guided by prevailing institutional protocols and contemporary international consensus guidelines, was uniformly administered to all participants. This encompassed timely institution of appropriate antimicrobial therapy, judicious intravenous fluid resuscitation, hemodynamic optimization (including vasopressor agents as indicated), definitive source control measures where applicable, and comprehensive supportive care for organ dysfunctions.

2.4. Data Acquisition and Monitoring

Upon enrolment, baseline data encompassing demographic variables, co-morbid conditions, putative or confirmed sources of infection, and initial SOFA scores were meticulously recorded. A panel of laboratory assessments, including full blood count, renal and hepatic function profiles (with specific attention to Alanine Transaminase - ALT), serum lactate, C-reactive protein (CRP), procalcitonin (PCT), creatine phosphokinase (CPK), and pertinent microbiological cultures (e.g., blood, urine, respiratory specimens), was conducted at baseline (day 1). Serial measurements of CRP, PCT, and lactate were performed on days 1 and 7 for protocol-mandated analysis.

Vigilant monitoring for adverse events was maintained throughout the study, with particular attention to potential hepatotoxicity (defined as ALT elevation >5 times ULN from baseline or de novo icterus) and myopathy/myositis (new-onset myalgia or muscular weakness accompanied by CPK elevation >500 U/L). Occurrence of such an event, if deemed attributable to atorvastatin, prompted discontinuation of the investigational product. All participants were

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followed until 28 days post-randomization or until death, if earlier. Participants discharged prior to day 28 were contacted via telephone on the 28th day to ascertain their status.

2.5. Study Endpoints

The primary measure of effectiveness in this study was all-cause mortality at 28 days post-randomization. Several key secondary endpoints were also assessed, including the proportion of surviving patients who required vasopressor support, renal replacement therapy, or mechanical ventilation beyond day 5 of enrollment. Additionally, researchers evaluated total hospital stay duration and changes in key inflammatory markers – specifically, absolute changes in CRP, procalcitonin (PCT), and serum lactate concentrations – from day 1 to day 7.

2.6. Sample Size Determination

A priori sample size estimation, predicated on the findings of Dobesh et al. (mortality rates of 48.4% vs. 31.7%), suggested a requirement for 134 participants per arm (total 268) to achieve 80% power at a two-sided alpha of 0.05.⁸ However, pragmatic considerations related to the finite one-year study duration and observed recruitment dynamics necessitated a recalibration of the target sample size to 60 participants (30 per arm), acknowledging the potential for an underpowered primary outcome assessment.

2.7. Statistical Methodology

Analyses were conducted following an intention-to-treat paradigm, encompassing all randomized participants within their assigned allocation groups. Descriptive statistics were employed to delineate baseline characteristics: continuous variables were summarized as means with standard deviations (SD) or medians with interquartile ranges (IQR), contingent upon normality assessed via the Shapiro-Wilk test; categorical variables were presented as frequencies and percentages. Inter-group comparisons at baseline utilized independent samples t-tests or Mann-Whitney U tests for continuous data, and Chi-square or Fisher's exact tests for categorical data, as appropriate.

The primary outcome, 28-day mortality, was analyzed using the Chi-square test, with the risk difference and its 95% confidence interval (CI) computed. Categorical secondary outcomes were similarly analyzed. For continuous secondary endpoints, inter-group differences in absolute changes (day 7 minus day 1 for biomarkers) or durations (LOS) were assessed using t-tests or Mann-Whitney U tests. Statistical significance was ascribed to p-values <0.05.

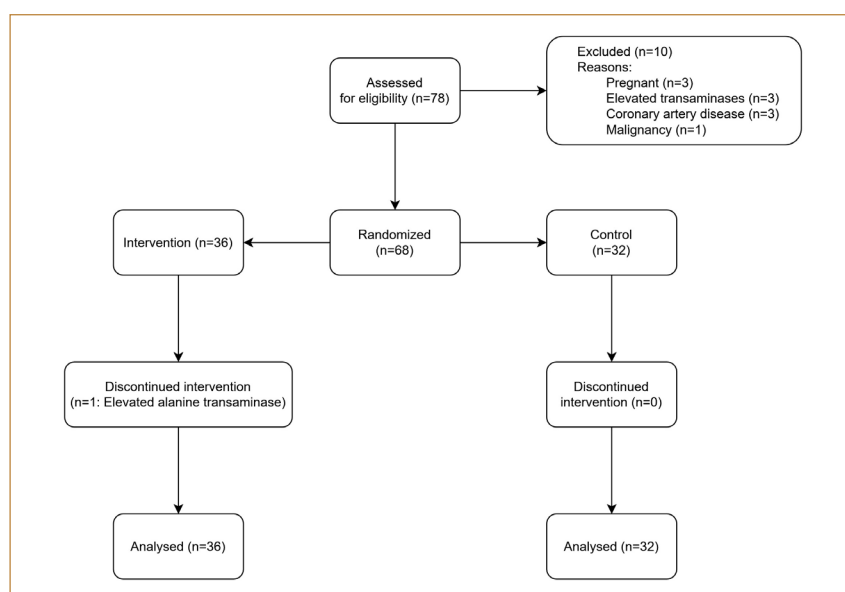


Figure 1. Flow diagram of the participants in the study

Results

3.1. Participant Recruitment and Baseline Profile

Over the 12-month recruitment period (January - December 2024), 78 patients presenting to the acute medical unit with suspected sepsis underwent eligibility screening. Of these, ten individuals were deemed ineligible due to: pregnancy (n=3), pre-existing significant transaminase elevation (n=3), chronic statin use for established coronary artery disease (n=3), or a diagnosis of lymphoma (n=1). Thus, 68 participants fulfilled the inclusion criteria and were subsequently randomized: 36 to the atorvastatin (intervention) arm and 32 to the standard care (control) arm (Figure 1). Within the atorvastatin cohort, one participant discontinued the study drug owing to transaminitis. All participants in the control arm completed the stipulated follow-up. The intention-to-treat analysis encompassed all 68 randomized individuals.

The baseline demographic and clinical attributes of the randomized cohorts are detailed in Table 1 and were generally well-matched. The median age was 57 years (IQR 44, 64) in the intervention group and 55 years (IQR 45, 60) in the control arm. Gender composition was comparable. Diabetes mellitus was present in a higher, albeit not statistically significant, proportion of participants in the atorvastatin group (64% vs. 41%, $p=0.055$). Other significant comorbidities, including chronic kidney and lung diseases, were similarly distributed. The respiratory tract was the predominant source of sepsis in both arms (89% intervention vs. 81% control). The admission SOFA score, indicative of initial illness severity, was median 8 (IQR 6.0, 9.0) for the atorvastatin group and 9 (IQR 6.0, 13.5) for controls ($p=0.15$). Initial concentrations

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Table 1. Baseline characteristics of the study participants

Characteristic	Overall N = 68 ¹	Control N = 32 ¹	Intervention N = 36 ¹	p-value ²
Age	55 (45, 61)	55 (45, 60)	57 (44, 64)	0.3
Gender				0.6
Female	32 (47%)	16 (50%)	16 (44%)	
Male	36 (53%)	16 (50%)	20 (56%)	
Comorbidities				
Diabetes mellitus	36 (53%)	13 (41%)	23 (64%)	0.055
Cerebrovascular accident	0	0	0	
Chronic kidney disease	15 (22%)	5 (16%)	10 (28%)	0.2
Chronic lung disease	11 (16%)	6 (19%)	5 (14%)	0.6
Source of sepsis: organ system involvement				
Respiratory system	58 (85%)	26 (81%)	32 (89%)	0.5
GIT & HPBS*	5 (7.4%)	3 (9.4%)	2 (5.6%)	0.7
Renal	34 (50%)	16 (50%)	18 (50%)	>0.9
Central nervous system	6 (9.1%)	5 (17%)	1 (2.8%)	0.084
SSTI [§]	11 (16%)	5 (16%)	6 (17%)	>0.9
Assessment-at-emergency admission				
SOFA score ³	8.0 (6.0, 12.0)	9.0 (6.0, 13.5)	8.0 (6.0, 9.0)	0.15
CRP (mg/l) ⁴	157 (84, 229)	158 (77, 218)	154 (92, 244)	0.9
ALT(u/l) ⁵	22 (12, 29)	22 (15, 29)	21 (10, 29)	0.5
Procalcitonin(ng/ml)	4 (1, 12)	3 (0, 13)	5 (1, 11)	>0.9
Lactate (mmol/l)	1.74(1.40,2.70)	1.70(1.38,2.80)	1.75(1.42,2.70)	>0.9
Vasopressor requirement	32 (47%)	18 (56%)	14 (39%)	0.2

¹Median (Q1, Q3); n (%) ²Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test *GIT&HPBS = Gastrointestinal and hepatopancreatic biliary system, [§]SSTI= Skin and soft tissue infections, ³SOFA = sequential organ failure assessment, ⁴CRP= C reactive protein, ⁵ALT=Alanine transaminase

of key inflammatory markers (CRP, procalcitonin, lactate) and the prevalence of vasopressor requirement at baseline were also analogous across the groups.

3.2. Microbiological Landscape

Overall, pathogenic organisms were isolated from blood cultures in 38% (25/68) of participants (40% intervention vs. 35% control). *Staphylococcus* species (constituting 44% of positive hemocultures) and Gram-negative bacilli (collectively 44%, including *Escherichia coli*, *Klebsiella* spp., *Acinetobacter baumannii*) represented the most frequent isolates. Uropathogens, predominantly Gram-negative, were identified in 16% (10/68) of cases. Among the 10 participants from whom endotracheal aspirates were cultured, 90% yielded microbial growth, with *Acinetobacter baumannii* being the predominant isolate (78% of positive aspirates).

3.3. Primary Endpoint Analysis

Regarding the primary endpoint, 28-day all-cause mortality was observed in 13 of 36 participants (36%) allocated to atorvastatin, versus 18 of 32 (56%) in the

control arm. This corresponded to an absolute risk reduction of 20% (95% CI -5% to 45%), a difference that did not achieve statistical significance (p=0.10) (Table 2).

3.4. Secondary Endpoint Analyses

No statistically robust distinctions were identified between the atorvastatin and control groups concerning the proportion of survivors requiring vasopressor support beyond day 5 (36% [8/22] vs. 59% [10/17], p=0.16), RRT beyond day 5 (23% [5/22] vs. 24% [4/17], p>0.99), or mechanical ventilation beyond day 5 (45% [10/22] vs. 63% [10/16], p=0.30). The median duration of hospitalization was 10 days (IQR 7-13) in the atorvastatin arm and 12 days (IQR 7-14) in the control arm (p=0.36).

Evaluation of inflammatory biomarker kinetics revealed that the median absolute decline in CRP concentrations from day 1 to day 7 was -62 mg/L (IQR -149 to -3) in the atorvastatin group versus -48 mg/L (IQR -84 to 0) in the control group (p=0.29). Conversely, a more pronounced and statistically significant attenuation in procalcitonin

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Table 2. Primary and secondary outcome data of the study				
Characteristic	Overall	Control	Intervention	p-value ²
Primary outcome				
28days mortality	31 / 68 (46%)	18 / 32 (56%)	13 / 36 (36%)	0.10
Secondary outcomes				
Vasopressor requirement (beyond day 5)	18 / 39 (46%)	10 / 17 (59%)	8 / 22 (36%)	0.16
RRT* requirements beyond day5	9 / 39 (23%)	4 / 17 (24%)	5 / 22 (23%)	>0.99
Mechanical ventilation requirement beyond day 5	20 / 38 (53%)	10 / 16 (63%)	10 / 22 (45%)	0.30
The absolute reduction in CRP [§]	-52 (-122 – 0)	48 (-84 – 0)	-62 (-149 – -3)	0.29
Absolute reduction in procalcitonin	-2 (-13 – 0)	0 (-1 – 10)	-8 (-24 – -1)	0.005
The absolute reduction in lactate	-0.71 (-1.47 – -0.16)	-0.62 (-0.71 – 0.48)	-0.95 (-1.73 – -0.58)	0.048
Duration of hospital stay	10 (7 – 14)	12 (7 – 14)	10 (7 – 13)	0.36

*RRT=Renal Replacement Therapy, §CRP= C-reactive protein

concentrations was evident in the atorvastatin cohort (median change -8 ng/ml, IQR -24 to -1) compared to the control group (0 ng/ml, IQR -1 to 10) (p=0.005). Analogously, the median reduction in serum lactate levels was significantly greater in participants receiving atorvastatin (-0.95 mmol/L, IQR -1.73 to -0.58) relative to controls (-0.62 mmol/L, IQR -0.71 to 0.48) (p=0.048) (Table 2).

3.5. Safety and Tolerability

One participant (2.8%) in the atorvastatin arm experienced transaminase elevation (ALT >5 times ULN), which prompted discontinuation of the study medication. No instances of clinically overt myopathy necessitating drug cessation were recorded. No specific adverse drug reactions were identified within the control group.

Discussion

The present investigation, an open-label, randomized controlled evaluation of adjunctive atorvastatin in adult sepsis patients within an acute medical emergency context, failed to demonstrate a statistically significant advantage in reducing 28-day all-cause mortality. Furthermore, the intervention did not appreciably alter the requirements for protracted organ support or the overall duration of hospitalization. However, a salient observation was the significant attenuation of serum procalcitonin and lactate levels by day 7 in the atorvastatin-treated cohort, suggesting a potential favorable modulation of the host inflammatory and metabolic response.

The observed 28-day mortality rates (36% with atorvastatin vs. 56% control), while numerically favoring atorvastatin with an absolute risk reduction of 20%, did not achieve statistical significance. This lack of statistical power may be multifactorial. Foremost, the statistical power of our trial was substantially constrained by its modest sample size; the recruitment

of 68 participants fell considerably short of the initial projection needed to robustly detect the anticipated mortality difference based on prior literature. This inherent limitation tempers the definitiveness of our conclusions regarding mortality. Secondly, our therapeutic strategy involved acute statin initiation upon sepsis diagnosis. This contrasts with some observational studies reporting benefits, which often included patients already on chronic statin therapy, potentially deriving more established endothelial-protective and immunomodulatory effects.²⁰ Our findings align with several RCTs, such as the ASEPSIS trial (atorvastatin 40mg in ward sepsis patients) and the study by Kruger et al. (atorvastatin 20mg in ICU sepsis), neither of which demonstrated a mortality benefit.^{20,21} The observations pertaining to secondary clinical endpoints, such as organ support duration and hospital stay, also resonate with findings from other trials. While certain studies, for instance Mansur et al.'s investigation in ARDS patients, reported an increase in vasopressor-free days with simvastatin, these often involved populations with antecedent statin exposure or employed different study methodologies.²²

Of particular interest, however, was the discernible impact of atorvastatin on key inflammatory and metabolic biomarkers. The significant reduction in both procalcitonin and lactate levels by day 7 in the intervention group is noteworthy. Procalcitonin, an established surrogate for bacterial infection severity and systemic inflammation, typically shows declining levels with effective infection control and portends a better prognosis.^{23,24} Similarly, lactate, reflecting tissue hypoperfusion and metabolic dysregulation, is a robust prognostic indicator in sepsis.²⁵ The observed attenuation of these biomarkers intimates a potential capacity for atorvastatin to modulate underlying septic pathophysiology, possibly through its anti-inflammatory actions or by improving microcirculatory perfusion, even if these effects did not

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translate into significant improvements in the clinical endpoints measured within the power constraints of this study.²⁶ While Singh RK et al. noted a significant CRP reduction with atorvastatin 40mg in septic shock, their study population presented with considerably lower baseline CRP levels.²⁷ Our cohort exhibited markedly elevated baseline CRP (median ~157mg/L), and while a trend towards greater reduction was seen with atorvastatin, the difference was not statistically significant. The more pronounced PCT decline in our atorvastatin group is consistent with the known anti-inflammatory pleiotropy of statins.²⁸

Key methodological strengths of this trial encompass its randomized design, adherence to contemporary sepsis definitions, and the evaluation of both clinical and biochemical parameters in a resource-relevant emergency setting. Furthermore, comprehensive microbiological surveillance was undertaken.

Several limitations warrant acknowledgment. The modest sample size, as previously discussed, is the principal constraint, particularly impacting the power to detect differences in the primary mortality outcome. Secondly, the single-center design may curtail the external validity of our findings, although the diverse catchment area of our institution mitigates this to some extent. Thirdly, the unblinded nature of the trial introduces a potential for ascertainment or performance bias, though objective endpoints like mortality and laboratory values are less susceptible. Lastly, the 28-day follow-up window precludes assessment of longer-term sequelae.

Our study's findings are situated within a landscape of clinical equipoise, largely defined by the discordance between promising signals from observational studies and the predominantly neutral outcomes of randomized controlled trials.^{21,29,30} A primary unresolved issue is the distinction between de novo statin initiation in acute sepsis versus the continuation of chronic therapy.^{15,20} Current randomized data do not support routine de novo initiation of statins solely for sepsis treatment, whereas continuation of chronic statins appears reasonable barring contraindications; this aligns with mixed randomized controlled trial evidence and the absence of a guideline recommendation for statins as anti-sepsis therapy.^{14,31} Observational data, often suggesting a survival benefit, are susceptible to confounding by indication (the "healthy user effect"), as patients on chronic statin therapy may have a different baseline cardiovascular and inflammatory risk profile.^{30,32} In contrast, randomized controlled trials like the ASEPSIS trial, which focused on de novo initiation, failed to show a mortality benefit.²¹ Furthermore, the concept of a "one-size-fits-all" approach is increasingly challenged, and future research must explore

specific patient subgroups who may derive benefit. For instance, observational studies have hinted at advantages in hyper-inflammatory phenotypes or in cohorts with specific organ dysfunction, such as sepsis-associated ARDS.³³

Despite the conflicting evidence in the literature, the findings of our study offer a timely reminder of the potential benefits of statins in sepsis.³⁴ Our finding of significant reductions in procalcitonin and lactate suggests that patients with profound inflammatory and metabolic dysregulation at baseline could represent a target population. However, key unresolved practical questions remain for the acute physician. It is unclear if a potential survival advantage applies universally or is specific to certain patient subgroups defined by the source of infection, severity of illness, or inflammatory phenotype. The optimal agent, dose, and timing of administration also remain to be elucidated. Statin choice and dose may matter: atorvastatin has been studied at 20–40 mg in sepsis with neutral to favorable biomarker effects, whereas high-dose simvastatin has shown futility and potential harm signals in ICU infection cohorts.^{9,35} Addressing these granular questions through adequately powered, multicenter investigations, perhaps employing adaptive or biomarker-stratified designs, is imperative to definitively delineate any therapeutic niche for statins in the heterogeneous syndrome of sepsis.³⁴

In summation, in this randomized trial, adjunctive atorvastatin 20mg daily did not significantly alter 28-day mortality or the need for extended organ support in sepsis patients. However, the salutary effects on procalcitonin and lactate levels are intriguing and merit exploration in larger, more robustly powered, multicenter investigations to definitively delineate the therapeutic niche, if any, for statins as an ancillary intervention in the complex management of sepsis.

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Ethics Approval

Institutional Ethics Committee, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh (Ref: INT/IEC/2023/SPL-1137).

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Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request, following institutional data sharing policies.

Declaration

All named authors have reviewed and agreed to the submitted version of the paper; and that the material is original, unpublished and has not been submitted elsewhere.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Concept: SCS, Design: CAR and SCS, Literature search: CAR, Data acquisition: CAR, MSB, AS Statistical analysis: CAR and MKH, Manuscript preparation: CAR and SCS, Manuscript editing: NS, MKH, MSB and AS. All authors have reviewed and agreed to the submitted version of the paper, and agree to take responsibility for the integrity of the work as a whole.

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