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REVIEWER'S REPORT

Manuscript No.: IJAR-57692

Title: A FATAL PERIOPERATIVE STORM: SYNERGISTIC STATINÂ–HALOGENATED MYOTOXICITY WITH REFRACTORY HYPERKALAEMIA AND ACUTE KIDNEY INJURY Â— A CASE REPORT AND PROPOSED CLINICAL REASONING FRAMEWORK.

Recommendation:

Accept as it is .....

Accept after minor revision.....

Accept after major revision .....YES

Do not accept (*Reasons below*) .....

Rating	Excel.	Good	Fair	Poor
Originality		√		
Techn. Quality			√	
Clarity			√	
Significance			√	

Reviewer's ID: JPR-094

Detailed Reviewer's Report

 # Reviewer's Report

 # Overall Evaluation

This manuscript presents a clinically important and intellectually stimulating fatal case of postoperative rhabdomyolysis with refractory hyperkalaemia and acute kidney injury in a high-risk patient receiving chronic atorvastatin therapy and sevoflurane anaesthesia. The authors propose a mechanistic hypothesis of synergistic statin–halogenated anaesthetic myotoxicity and introduce a structured perioperative framework (STAT-OP).

The manuscript is well written, scientifically detailed, and supported by contemporary literature. However, several claims remain speculative and exceed the evidentiary strength of a single case report. Important diagnostic limitations, causality concerns, and over extension of recommendations must be addressed before publication.

 # Strengths

1. Clinically Significant Topic

*** Addresses a potentially under-recognized perioperative complication with fatal outcome.**

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*** Relevant to anaesthesiologists, intensivists, nephrologists, and perioperative physicians.**

2. Strong Pathophysiological Integration

*** Excellent integration of:**

*** statin myotoxicity,**
*** malignant hyperthermia biology,**
*** RyR1-mediated calcium dysregulation,**
*** AKI mechanisms,**
*** hyperkalaemia physiology.**

*** The mechanistic synthesis is sophisticated and educational.**

3. High-Quality Literature Support

*** References are current and largely appropriate.**
*** Incorporates recent evidence (2024–2025) and guidelines.**

4. Detailed Clinical Documentation

*** Chronology is clear.**
*** Laboratory findings and perioperative details are adequately described.**
*** Differential diagnosis discussion is reasonably thorough.**

5. Novel Conceptual Framework

*** The proposed "STAT-OP" framework is innovative and may stimulate future research and pharmacovigilance efforts.**

6. Educational Value

*** The manuscript has substantial teaching value regarding:**

*** perioperative rhabdomyolysis,**
*** hyperkalaemia management,**
*** risk stratification,**
*** limitations of intermittent haemodialysis.**

 # Weaknesses

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1. Overstatement of Causality

The manuscript repeatedly implies a probable causal synergistic interaction between statins and halogenated anaesthetics without direct proof.

Major missing evidence:

*** No muscle biopsy,**
*** No autopsy,**
*** No genetic testing,**
*** No in vitro contracture testing,**
*** No atorvastatin serum levels,**
*** No confirmation of malignant hyperthermia susceptibility.**

Thus, the mechanistic conclusions remain speculative.

2. Excessive Extrapolation from a Single Case

The proposed STAT-OP framework appears too definitive for hypothesis-generating evidence.

Statements such as:

*** "prefer TIVA in highest-risk patients"**
*** "structured perioperative surveillance"**
*** "low threshold for HCO-RRT"**

are insufficiently supported by one observation.

3. Differential Diagnosis Not Fully Excluded

Alternative explanations remain plausible:

*** prolonged positioning injury,**
*** diabetic metabolic crisis,**
*** ischemic muscle injury,**
*** occult sepsis,**
*** myocardial injury-related shock,**
*** medication interactions,**
*** perioperative hypoperfusion.**

The manuscript should better acknowledge multifactorial uncertainty.

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4. Possible Publication Bias Toward Hypothesis Construction

The discussion occasionally reads more like a narrative review or mechanistic essay than a CARE-compliant case report.

The discussion section is disproportionately long relative to the clinical data.

5. Limited Novelty

A similar statin–anaesthetic rhabdomyolysis interaction has already been described in previous literature (Reference 10).

The novelty lies mainly in:

*** integrative synthesis,**
*** expanded mechanistic discussion,**
*** proposed framework.**

6. Unsupported Recommendations

Recommendation of:

*** pharmacogenomic screening,**
*** routine biochemical surveillance,**
*** TIVA preference,**
*** continuous high cut-off RRT**

may not be practical, evidence-based, or guideline-supported for routine perioperative care.

 # Key Points

Major Scientific Points

1. Suggests a possible synergistic interaction between statins and volatile anaesthetics.
2. Highlights delayed postoperative rhabdomyolysis without classic malignant hyperthermia.
3. Emphasizes refractory hyperkalaemia as the terminal event.

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4. Discusses limitations of conventional intermittent haemodialysis in myoglobin clearance.
5. Proposes perioperative risk stratification model (STAT-OP).

Major Methodological Concerns

1. Single-patient observational evidence.
2. No confirmatory genetic or pathological testing.
3. Hypothesis exceeds available proof.
4. Clinical recommendations may overreach available data.

 # Significance

Clinical Significance: Moderate to High

*** Raises awareness of a potentially catastrophic perioperative complication.**
*** Encourages vigilance in high-risk statin-treated patients.**

Scientific Significance: Moderate

*** Hypothesis-generating rather than practice-changing.**
*** Valuable for future translational and pharmacovigilance studies.**

Educational Significance: High

*** Excellent educational review of rhabdomyolysis mechanisms and perioperative management.**

Novelty: Moderate

*** The synergistic hypothesis is not entirely novel.**
*** The structured framework and integrative synthesis provide incremental originality.**

 # Specific Recommendations for Revision

Major Revisions Required

1. Reduce Causal Language

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Replace:

*** "synergistic toxicity"**
with:
*** "possible association,"**
*** "hypothesized interaction,"**
*** "putative synergistic mechanism."**

2. Temper Clinical Recommendations

Avoid guideline-like recommendations from a single case report.

3. Expand Differential Diagnosis Discussion

Include:

*** pressure-induced rhabdomyolysis,**
*** occult myocardial ischemia,**
*** perioperative shock states,**
*** diabetic metabolic factors.**

4. Clearly Separate Evidence from Hypothesis

Distinguish:

*** established evidence,**
*** biologically plausible speculation,**
*** author opinion.**

5. Shorten Discussion

The manuscript would benefit from condensation of:

*** mechanistic repetition,**
*** pharmacogenomic speculation,**
*** extensive theoretical extrapolation.**

6. Improve CARE Compliance

Include:

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*** timeline table,**
*** medication chronology,**
*** fluid balance,**
*** urine output trend,**
*** perioperative CK trends if available.**

 # Minor Comments

1. Correct minor formatting inconsistencies.
2. Some sentences are excessively long and dense.
3. Consider simplifying terminology for broader readability.
4. Figure 2 may appear overly mechanistic/speculative for a case report.
5. Reference formatting should be carefully checked for journal style compliance.

 # Final Recommendation

Recommendation: MAJOR REVISION

Justification

The manuscript is scientifically interesting, clinically relevant, and well researched. However:

*** causality is overstated,**
*** speculative interpretations dominate parts of the discussion,**
*** recommendations exceed evidence strength,**
*** and important alternative explanations remain insufficiently addressed.**

After substantial revision emphasizing hypothesis-generating interpretation rather than inferred causation, the manuscript could become a valuable educational and discussion-provoking publication.

Major Revision Justification with Issue and Reason (Line-by-Line)

Line No.	Issue Identified	Reason for Major Revision
6–9	Overstatement of perioperative interaction	The manuscript implies a clinically established interaction between statins and halogenated

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Line No.	Issue Identified	Reason for Major Revision
	significance	anaesthetics without sufficient epidemiological or mechanistic proof. Stronger evidence is required before suggesting integration into routine risk stratification.
10–20	Single case used to support broad mechanistic conclusions	The report is based on one patient only; therefore, conclusions regarding synergistic toxicity remain hypothesis-generating rather than confirmatory.
21–26	"Six convergent injurious pathways" presented as causal explanation	The wording suggests causality despite absence of confirmatory diagnostics such as biopsy, autopsy, pharmacogenomics, or toxicological analysis.
24–26	STAT-OP framework introduced as clinical strategy	The proposed framework is insufficiently validated and may overextend beyond evidence available from a single case report.
30–33	Introductory section excessively detailed for a case report	The manuscript begins to resemble a narrative review rather than a concise CARE-compliant case report. Condensation is needed.
35–42	Mechanistic discussion presented with excessive certainty	Although biologically plausible, direct linkage between volatile anaesthetics and delayed rhabdomyolysis in this patient is unproven.
43–49	Genetic polymorphism discussion lacks patient-specific evidence	SLCO1B1, RYR1, and CACNA1S polymorphisms are discussed extensively despite absence of genetic testing in the patient.
47–49	"Biologically inevitable" statement is scientifically overstated	This phrase exaggerates the certainty of interaction and requires more cautious language.
50–54	Contradictory interpretation of guidelines	Current guidelines support statin continuation because benefits outweigh risks; manuscript insufficiently balances this established evidence with speculative toxicity concerns.
56–60	"Produced a fulminant, refractory and lethal trajectory"	Multifactorial contributors exist; manuscript attributes excessive causal weight to statin–anaesthetic synergy.
62–76	Important baseline information incomplete	Missing baseline CK/CPK, liver enzymes, perioperative fluid balance, urine output trend, and detailed medication chronology reduce interpretability.
79–85	Intraoperative monitoring details limited	More detailed haemodynamic trends, blood loss, fluid administration, arterial blood gas values, and urine output are needed to exclude other causes of

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Line No.	Issue Identified	Reason for Major Revision
		rhabdomyolysis.
86–94	Differential diagnosis incompletely explored	Alternative causes such as prolonged positioning injury, occult ischemia, diabetic metabolic crisis, compartment syndrome, or perioperative hypoperfusion are insufficiently evaluated.
95–99	Dismissal of myocardial infarction may be premature	Elevated troponin with cardiomyopathy requires more robust exclusion of myocardial ischemia or perioperative infarction.
103–105	Management details insufficient	Dialysis modality, duration, membrane type, fluid volume, vasopressor dose, and electrolyte correction protocol require clarification.
106–109	Rebound hyperkalaemia interpretation incomplete	Persistent muscle necrosis, inadequate clearance, metabolic instability, or severe cardiogenic shock may independently explain rebound hyperkalaemia.
114–119	"Paradigmatic instance" wording exaggerated	A single observation cannot define a new perioperative phenotype. Language should be moderated.
121–135	Mechanistic synthesis excessively speculative	The proposed mechanistic cascade is biologically plausible but unsupported by direct experimental or patient-specific evidence.
124–125	Genetic association data overinterpreted	Population-level genetic associations cannot be directly extrapolated to this patient without testing confirmation.
127–130	AIR phenotype assignment speculative	Patient lacked classical malignant hyperthermia findings and no confirmatory contracture testing was performed.
131–134	Mechanistic conclusion stated as established fact	The manuscript should distinguish hypothesis from demonstrated causation.
137–145	Multiple cofactors acknowledged but not quantitatively analyzed	Relative contribution of diabetes, cardiomyopathy, polypharmacy, positioning, and anaesthesia remains uncertain.
147–149	Recommendation for systematic surveillance unsupported	Routine postoperative CK/electrolyte surveillance is not evidence-based for general statin-treated surgical populations.
150–156	Renal replacement discussion exceeds scope of case report	HCO dialysis recommendations are based on limited evidence and should not be presented as preferred management strategy from one case.

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Line No.	Issue Identified	Reason for Major Revision
157–158	Guideline integration incomplete	The EAST guideline recommendations are summarized without adequate contextual discussion regarding clinical applicability.
161–185	STAT-OP framework insufficiently validated	The framework resembles a clinical guideline despite absence of validation studies or consensus recommendations.
164–170	Pharmacogenomic testing recommendations premature	Routine SLCO1B1 and RYR1 screening is not currently recommended in perioperative practice and lacks cost-effectiveness evidence.
172–174	Recommendation favoring TIVA over volatile anaesthesia unsupported	No comparative perioperative evidence demonstrates superiority of TIVA specifically for prevention of statin-associated rhabdomyolysis.
178–180	Serial CPK recommendations not evidence-based	Proposed monitoring protocol lacks validation and may not be practical or cost-effective.
184–185	ICU and HCO-RRT recommendations overgeneralized	Recommendations appear stronger than evidence permits and should be presented as speculative considerations only.
187–193	Limitations acknowledged but insufficiently emphasized	Major missing diagnostic investigations significantly weaken causal inference and should be discussed more prominently.
193–195	Claim of coherent mechanistic model	The model remains theoretical and requires validation through larger observational or translational studies.
197–205	Conclusions stronger than evidence permits	Conclusions imply probable causality and actionable management changes despite single-case observational design.
202–205	Practice recommendations overextended	Recommendations regarding TIVA, pharmacogenomics, and high cut-off RRT require stronger evidence before clinical endorsement.
206–208	"Clinically meaningful, potentially preventable phenotype"	Preventability has not been demonstrated and statement may overstate findings.
Entire Discussion	Discussion disproportionately long	The manuscript functions partly as a mechanistic review article rather than a focused case report; shortening is required.
Entire Manuscript	CARE reporting incompletely fulfilled	Important supportive clinical details, laboratory trends, and perioperative management data are

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Line No.	Issue Identified	Reason for Major Revision
		missing.
Figures 1–2	Figure 2 overly speculative	Proposed pathophysiological model visually reinforces unproven causality and should be clearly labeled as hypothetical.
References	Heavy reliance on mechanistic extrapolation	Several recommendations are derived indirectly from mechanistic or observational literature rather than direct clinical evidence.

Overall Justification for Major Revision

Major revision is warranted because the manuscript presents an important and potentially valuable clinical observation but currently overstates causality, extrapolates beyond available evidence, and proposes partially unvalidated clinical recommendations from a single case report. Significant revision is needed to:

reduce speculative language,

strengthen differential diagnosis discussion,

improve methodological transparency,

clarify hypothesis-generating nature,

and align conclusions with the evidentiary limitations of the report.