Sequence Matters in Modelling Combined Injury: Burn-First Combined Injury Amplifies Gastrointestinal Acute Radiation Syndrome

Zamantha Manalansan-Roberson

Ops in a Nuclear Environment: Ensuring Medical Readiness & Preparing for Complex Injuries

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USU Uniformed Services University

AFRRI Uniformed Services University

Non-Disclosures and Disclaimers

- Zamantha Manalansan-Roberson has no conflicts to report

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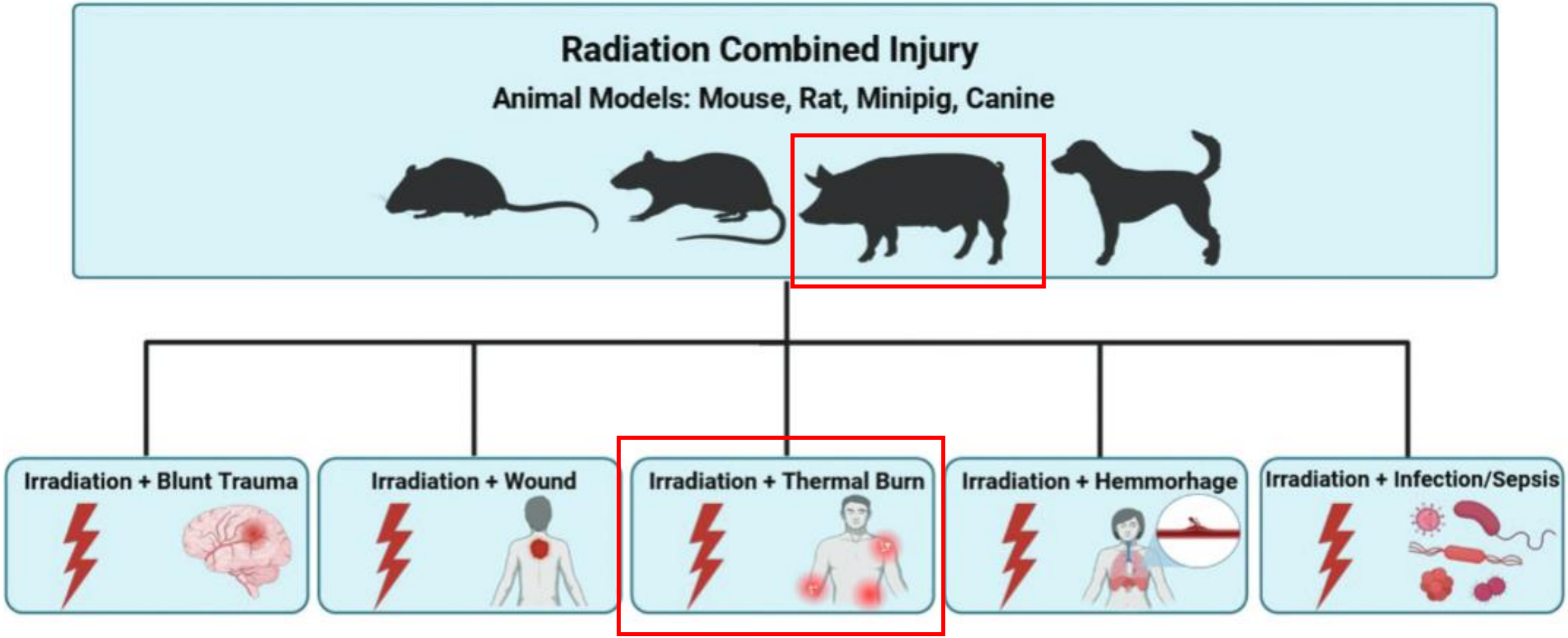
Introduction

- ~50% of casualties from a nuclear detonation may experience combined radiation and thermal injury.
- Understanding CI severity is critical for improving diagnosis, triage, and countermeasure development.

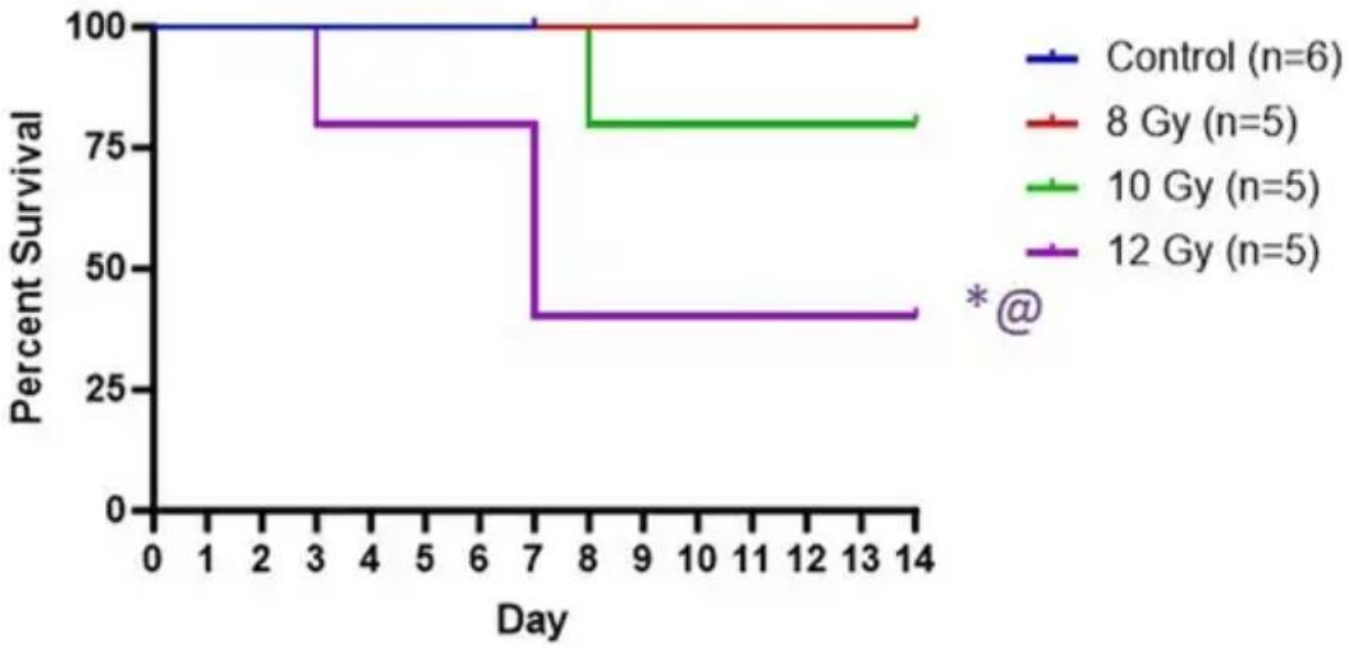
Nagasaki (*Pew Research, 2025)*

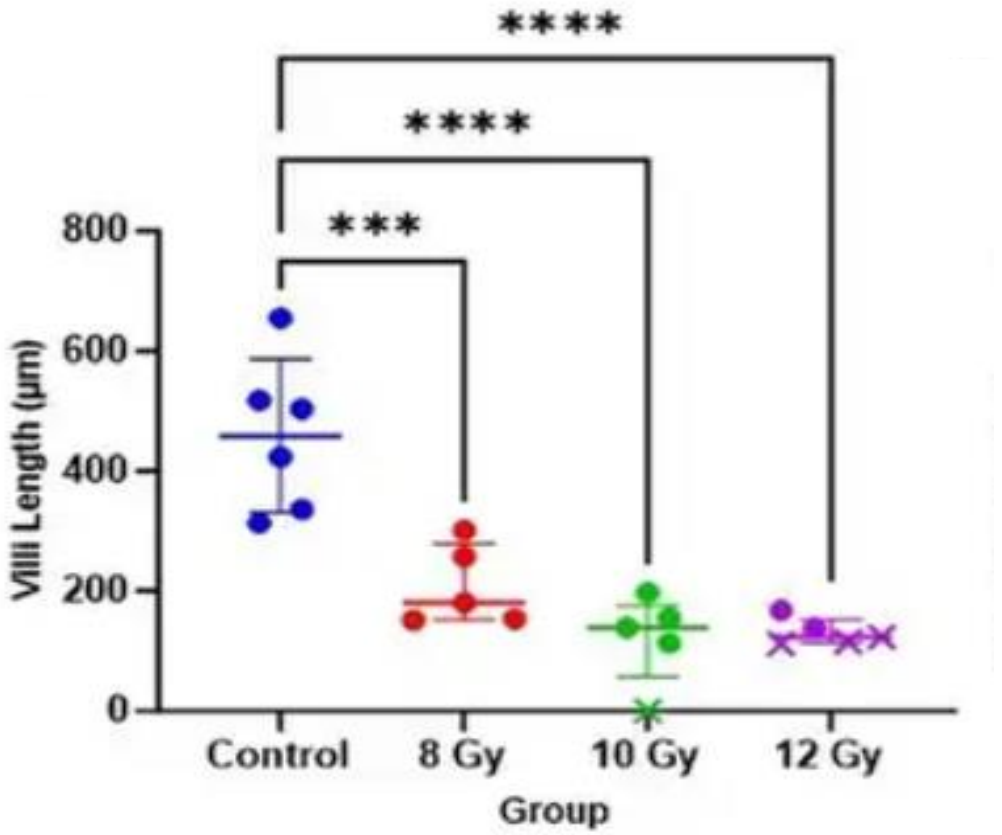
Modeling Combined Injury (CI)



Singh, V. K., & Seed, T. M. *Expert Opinion on Drug Discovery* (2025).

GI-ARS in Sexually Mature Male Minipigs

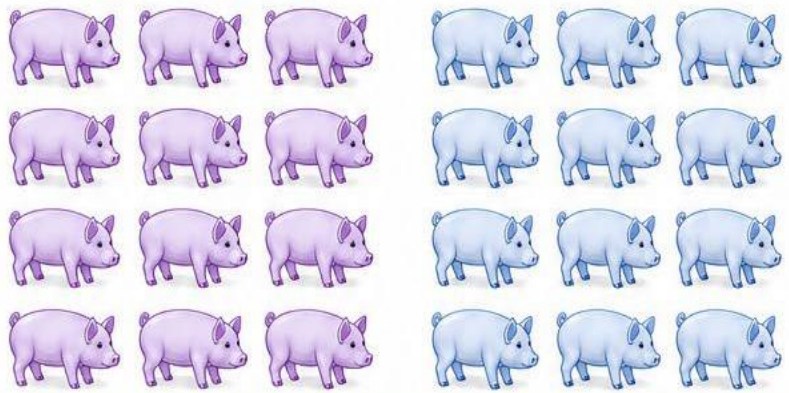




Horseman, T., et al., *Shock* (2024).

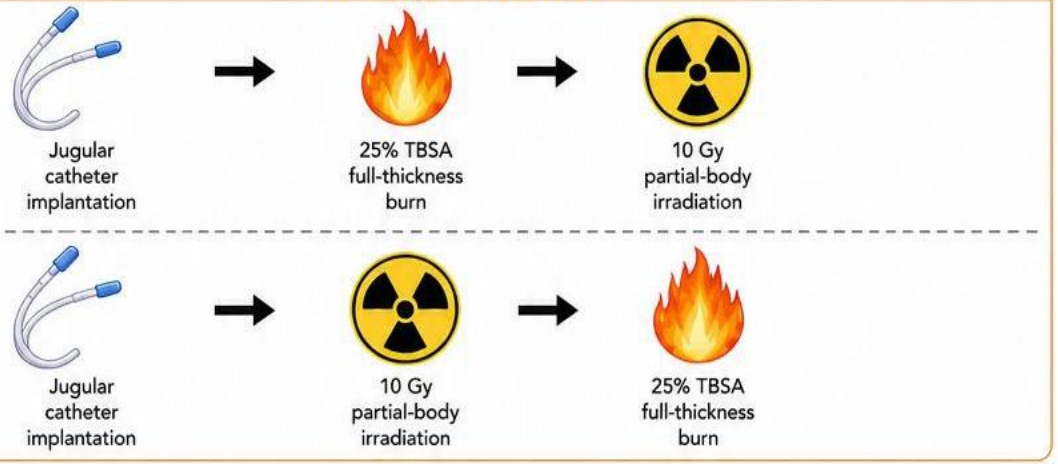
Experimental Design and Timeline

1. Animal Groups

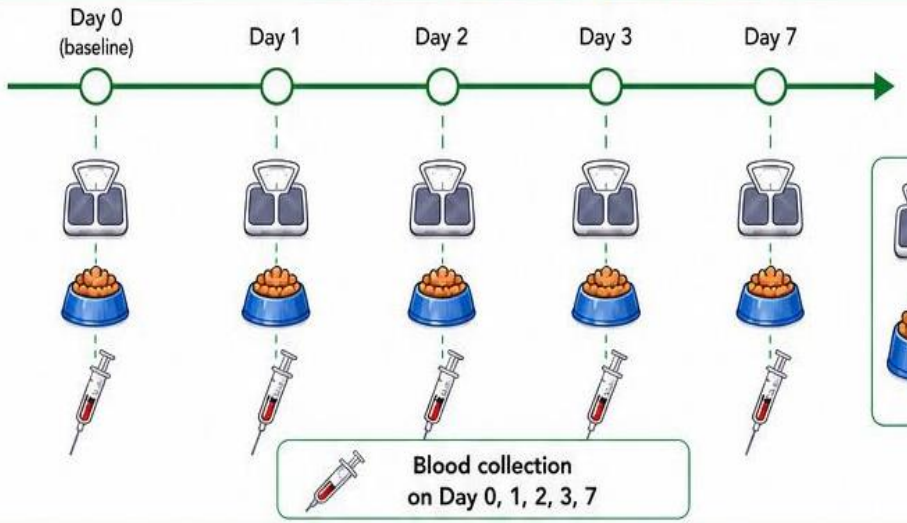


Male Sinclair pigs
(n = 24 total)

2. Injury Procedures



3. Monitoring & Sampling Timeline



4. Endpoint & Analysis

Clinical observations (every day)

Clinical End Points

SWINE PAIN/DISTRESS ASSESSMENT SCORE SHEET

Pr

Parameter	Animal ID:_____ PI:_____	Date Scor	D0	D1 AM	D1 PM	D2 AM	D2 PM	D3 AM	D3 PM	D4
General Appearance	Normal (eyes/nose clear, relaxed posture)	0								
	Abnormal Posture (hunched back, leaning for support, shifting weight), increased respiratory rate, skin discoloration (blotchy)	2								
	Fixed gaze, persistent twitching or trembling, excessive foaming at mouth, hyperventilation w/mouth breathing, head	3								
Natural Behavior	Normal (playing, foraging, rooting, standing, social interaction with observer)	0								
	Less active, lethargic/depressed, decreased social interaction with observer (isolated at	2								
	Inactive, recumbent, increased vocalization/moaning, esp when	3								
Fecal/Urinary Output	Normal (multiple piles of feces, urine present)	0								
	Decreased (≤ 1 pile feces, only small amount of urine)	1								
	Absent or severely decreased, watery/bloody diarrhea	3								
*Body Weight	Initial _____kg	0	___ kg	___ kg	___ kg	___ kg	___ kg	___ kg	___ kg	___ kg
	3-9% total wt loss, BCS 2	1								
**Body Condition Score (BCS)	10-19% BW loss	2								
	≥10% wt loss in a 24 hour period or ≥20% total wt loss, BCS 1	3	___% BWL	___% BWL	___% BWL	___% BWL	___% BWL	___% BWL	___% BWL	___ BW
Appetite	Normal appetite, eats all enrichment	0								
	Reduced appetite, eats some enrichment	1								
	No appetite, not eating enrichment	3								
Wound Assessment	None/healed	0								
	Mild redness, +/- swelling	1								
	Moderate redness, +/- swelling	2								
	Discharge, necrosis, dehiscence (possible	3								
Mobility/ Lameness	Normal ambulation	0								
	Slight lameness in one/both legs, short periods of standing/walking (unassisted)	1								
	Lame, limited ability to stand and walk (assisted)	2								
	Recumbent – little response when prodded	3								

Hypothesis

We hypothesized that thermal burn injury preceding radiation exposure would induce immune priming, resulting in a protective effect that attenuates gastrointestinal acute radiation syndrome (GI-ARS) and intestinal injury compared with radiation-first combined injury.

Burn-first worsens GI symptoms

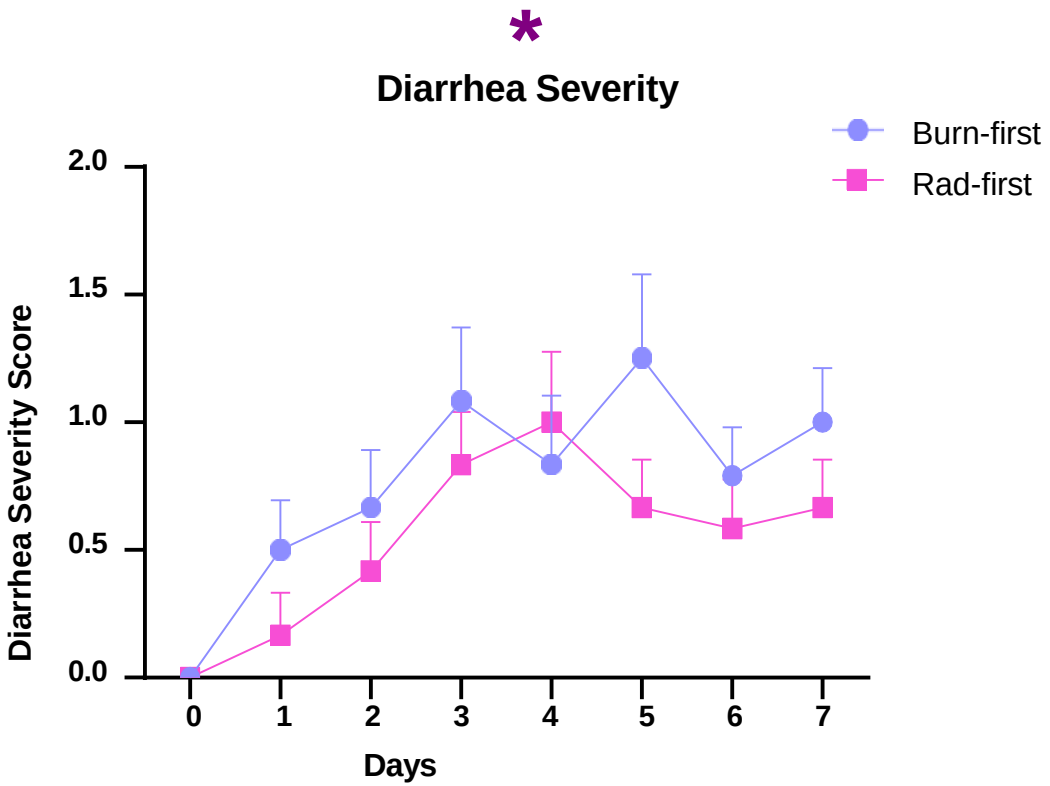


Fig. 1. Burn-first animals exhibited greater diarrhea severity over time compared with radiation-first animals, with a significant effect of injury order (P = 0.0368).

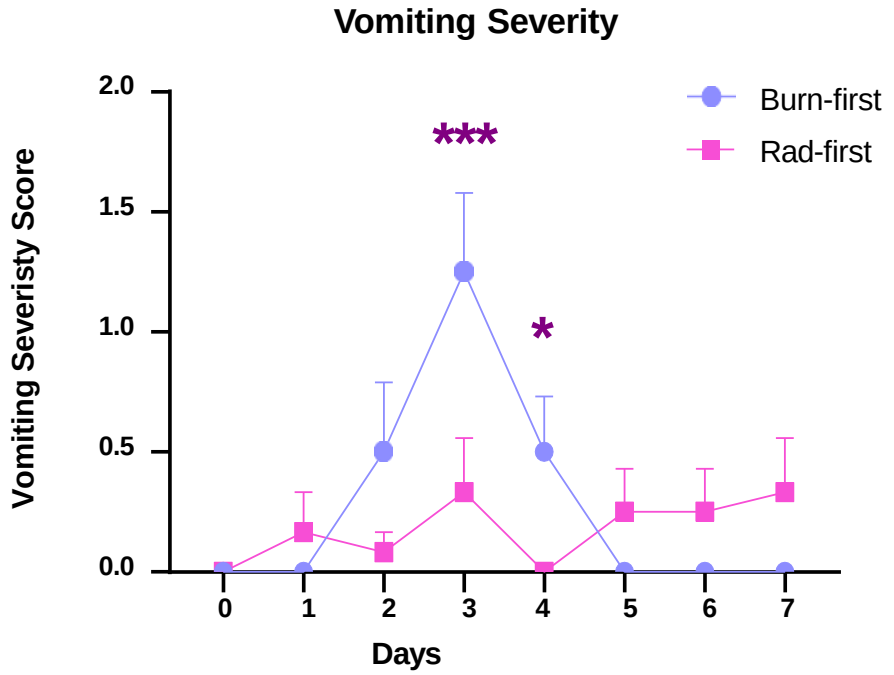


Fig. 2. Burn-first animals exhibited greater vomiting severity early after injury, with a significant time × injury order interaction (P = 0.0009). Post hoc analysis showed higher vomiting scores in the burn-first group on Day 3 (P = 0.0001) and Day 4 (P = 0.0353), with peak vomiting observed on Day 3.

Appetite and Consequences

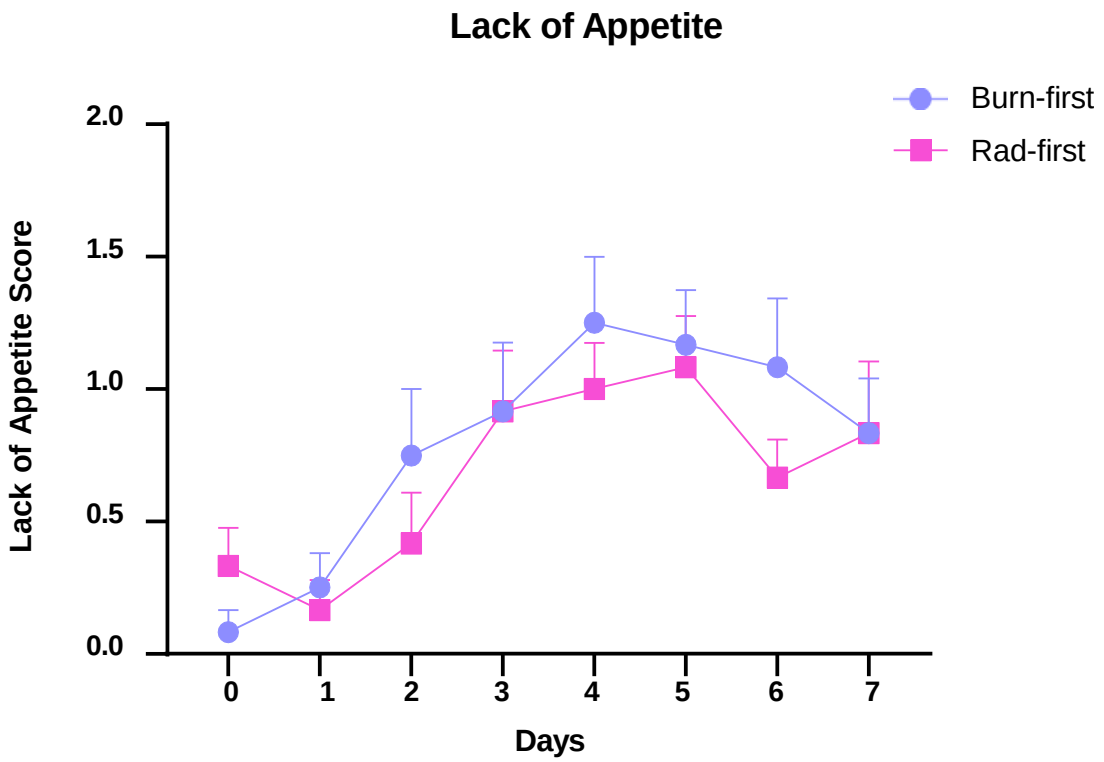


Fig. 3. Appetite declined significantly over time (P < 0.0001) but was not affected by injury order (P = 0.5033), with no significant time × injury order interaction (P = 0.5944).

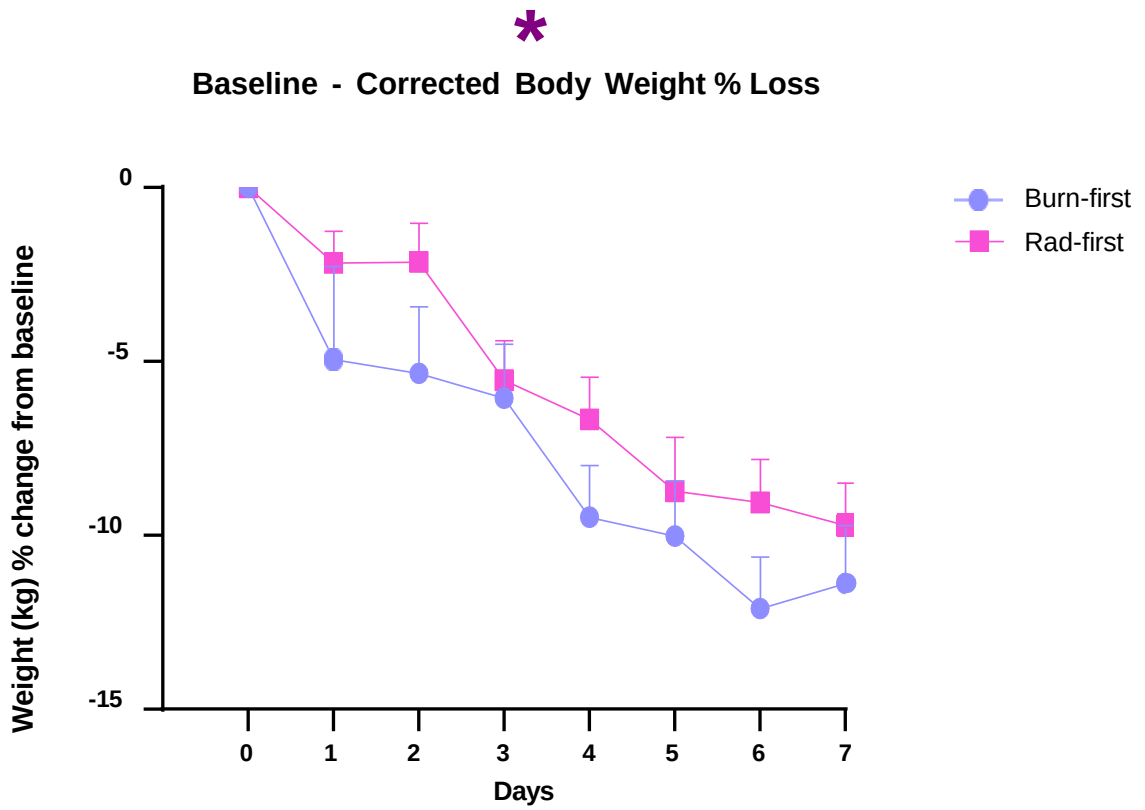


Fig. 4. Burn-first animals exhibited greater baseline-corrected body weight loss compared with radiation-first animals. Body weight was significantly affected by day (P < 0.0001) and injury order (P = 0.0083), with burn-first animals showing lower body weight across time points (mean difference = −1.916, 95% CI: −3.333 to −0.4987).

Molecular Endpoints

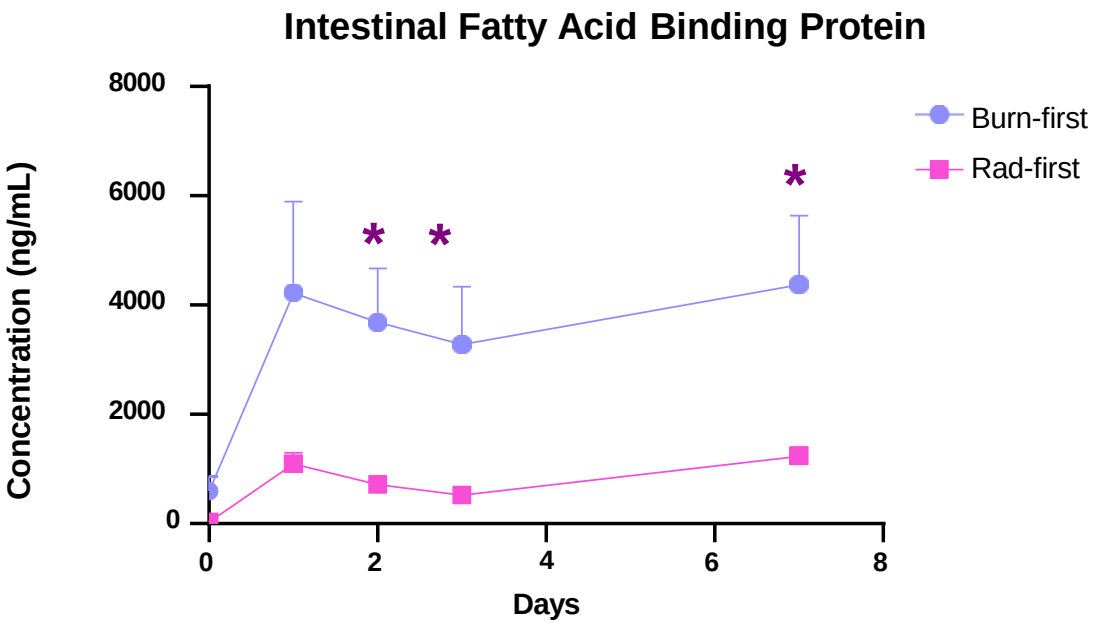


Fig. 5. Burn-first animals exhibited increased intestinal injury, demonstrated by elevated I-FABP levels compared with radiation-first animals. Mixed-effects analysis identified significant effects of time (P = 0.0050) and injury order (P = 0.0058). Post hoc analysis showed higher I-FABP levels in the burn-first group on Day 2 (P = 0.0127), Day 3 (P = 0.0239), and Day 7 (P = 0.0308).

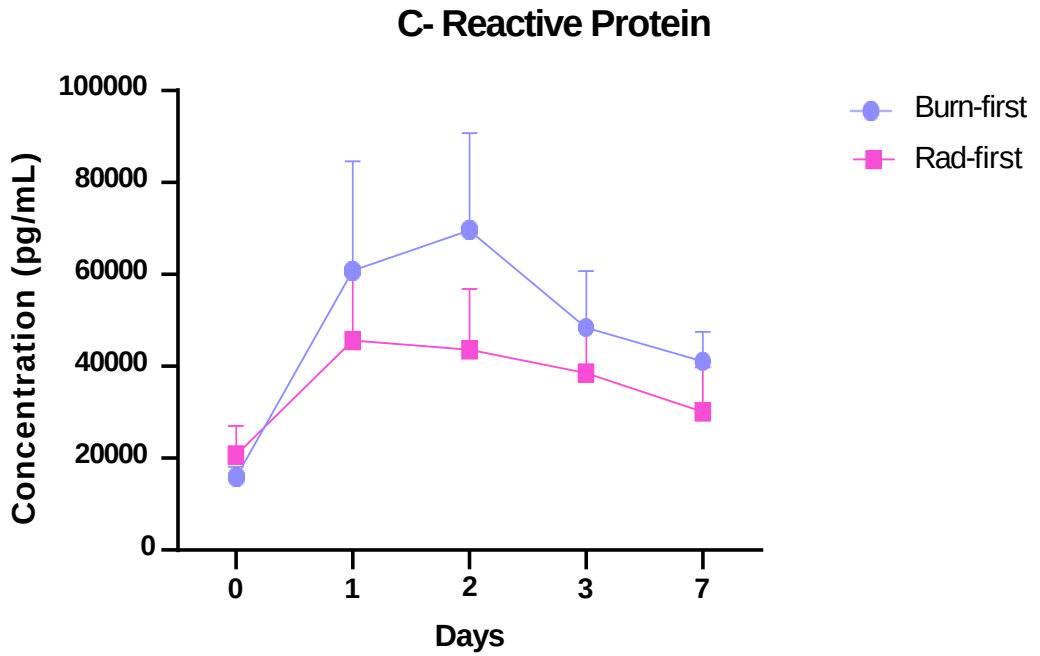


Fig. 6. Burn-first animals exhibited elevated systemic inflammation, demonstrated by increased CRP levels compared with other injury-order groups. Mixed-effects analysis identified significant effects of time (P = 0.0492) and injury order (P = 0.0124).

Conclusion and Take Home

- Burn-first + radiation worsened GI-ARS (↑ vomiting and diarrhea) compared with radiation-first injury.
- Burn-first animals demonstrated:
  - ↑ Weight loss
  - ↑ Intestinal injury (I-FABP)
  - ↑ Systemic inflammation (CRP)
- Injury sequence should be considered in CI model development to improve diagnostics and countermeasure strategies.

Future Directions

Identify Mechanisms

- Immune Dysregulation
- Inflammatory Signaling – (cytokines – IL-18, IL-6)

Validate Biomarkers

- Histological Damage– (villi lengths, TJPs)
- Progression of GI microbiome

Improve Clinical Management

- Better triage and treatment strategies for CI

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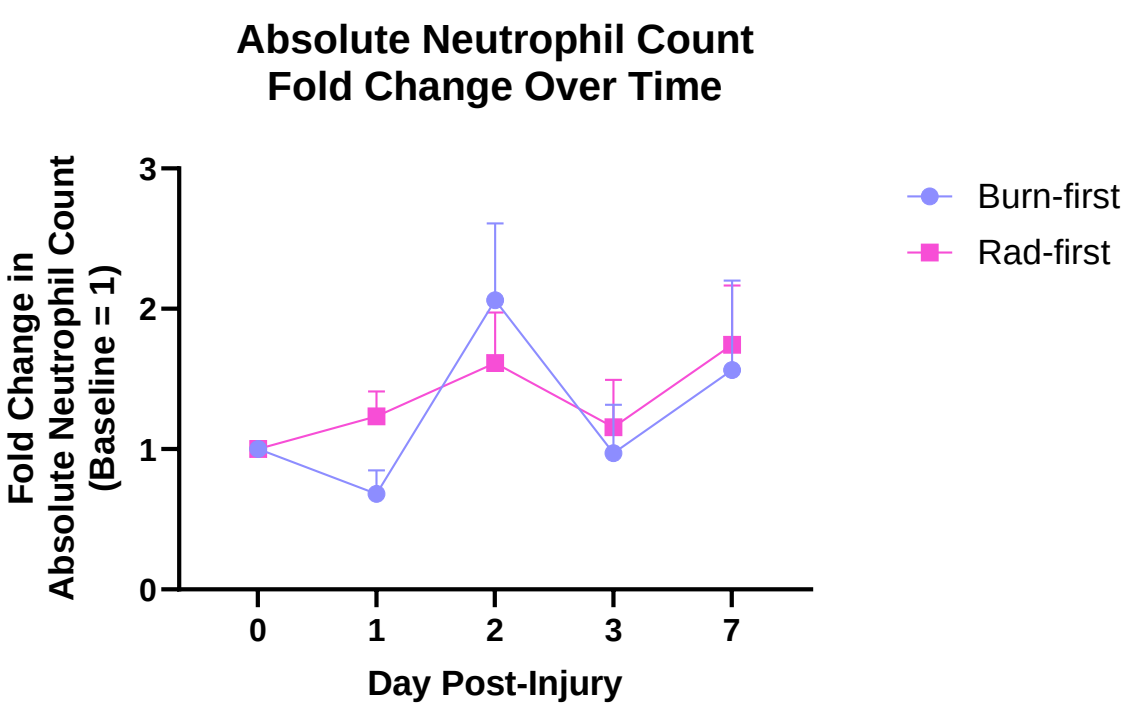
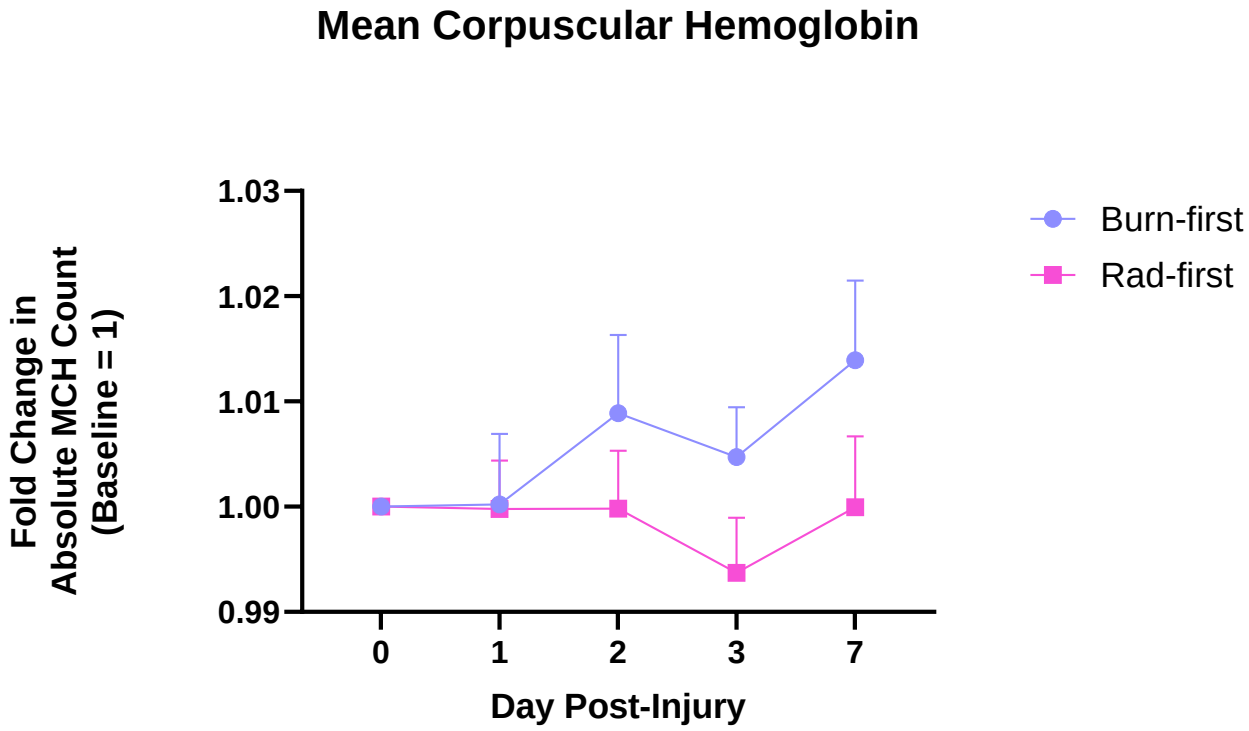

Absolute Neutrophil Count
Fold Change Over Time
Fold Change in
Absolute Neutrophil Count
(Baseline = 1)
3
2
1
0
0
1
2
3
7
Day Post-Injury
Burn-first
Rad-first


Mean Corpuscular Hemoglobin
Fold Change in
Absolute MCH Count
(Baseline = 1)
1.03
1.02
1.01
1.00
0.99
0
1
2
3
7
Day Post-Injury
Burn-first
Rad-first