Comparative analysis of total and partial body irradiation in nonhuman primates over 60 days in urine, serum, and saliva

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Abstract

Motivation - Timely assessment and management of individuals following radiological incidents is a critical capability supporting national security objectives. In a radiological or nuclear event, realistic exposures may incur differential doses to organs and bone marrow. Existing radiation exposure biomarkers, however, do not account for partial body shielding and bone marrow sparing.

Methods - In this study, male and female nonhuman primates (NHPs) were either total body irradiated (TBI) with 5.5 Gy or partial body irradiated (PBI) with 5.5 Gy and 5% bone marrow shielding. Serum, saliva, and urine were collected pre-exposure and up to 60 days following irradiation. Biomarkers listed in previous TBI studies were identified and analyzed in PBI populations. Untargeted metabolomic analysis through liquid chromatography high resolution time-of-flight mass spectrometry (LC-MS) was performed on all three biofluids.

Results & Conclusions - Receiver operating characteristic (ROC) curves show altered urinary response over time. Principal component analysis (PCA) illustrates unique behavior of TBI biomarkers in PBI samples. Results reinforce significance of hematopoietic and gastrointestinal (GI) acute radiation syndromes for medical management.

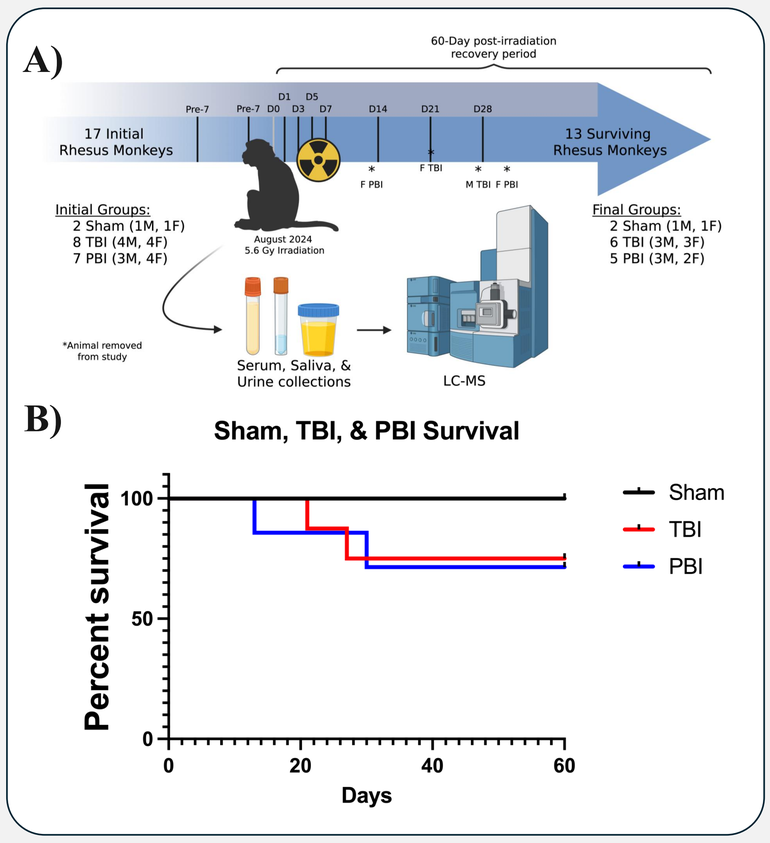
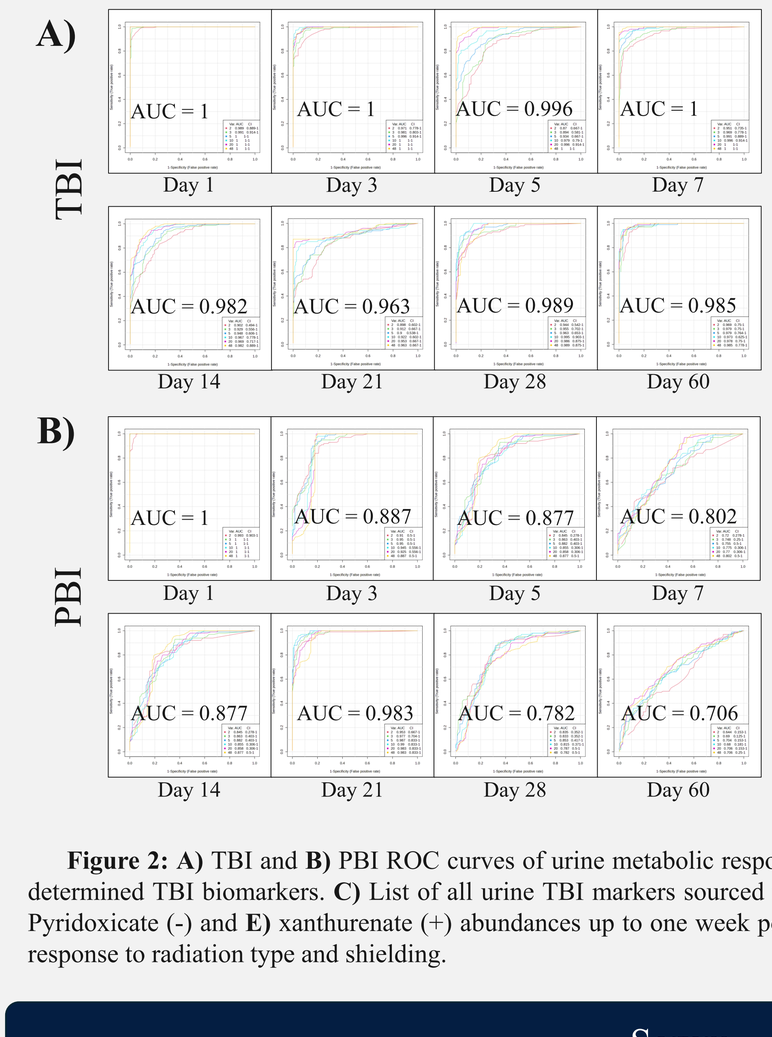


Figure 1: A) Experimental setup and sample collection times. Three NHPs met euthanasia criteria, four were removed from study. **B)** Kaplan Meier curve depicts survival rates for all cohorts over 60-day post-irradiation period. Graphics created with BioRender.com.

Urine



C)

Urine Markers					
Cortisone_pos	Xanthurenate_pos	7-methylguanine_pos	Urate_neg	Oxoglutarate_neg	Xanthosine_neg
Kynurenate_pos	7-Methylguanine_pos	Xanthurenate_neg	L-Alanine_neg	Citrate_neg	Creatine_pos
Propionylcarnitine_pos	L-Acetylcarnitine_pos	Taurine_neg	Pantothenate_neg	Xanthine_neg	Hypoxanthine_pos
Cortisol_pos	Isobutyryl-L-Carnitine_pos	cis-Aconitate_neg	Azelaate_neg	Fumarate_neg	4-Pyridoxicate_neg
L-Cartinine_pos	Cortisone_pos	Malate_neg	Hexanoylglycine_neg	Methylmalonate_neg	

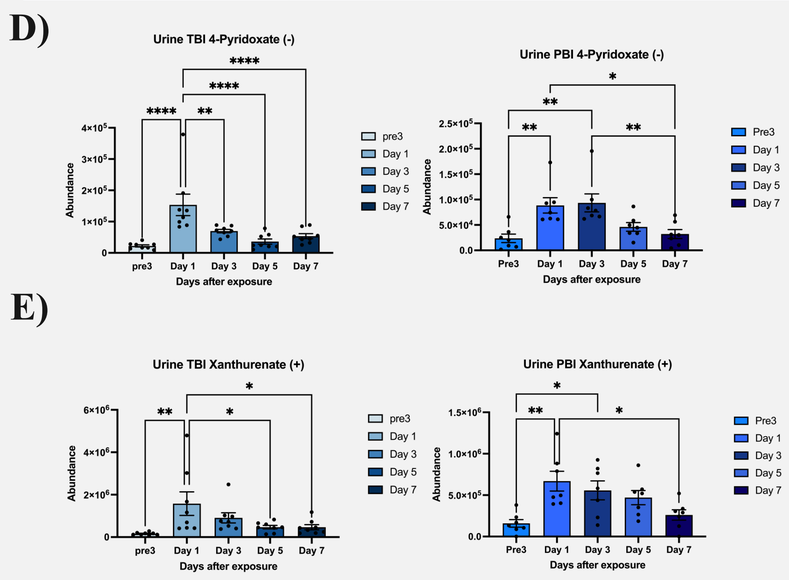
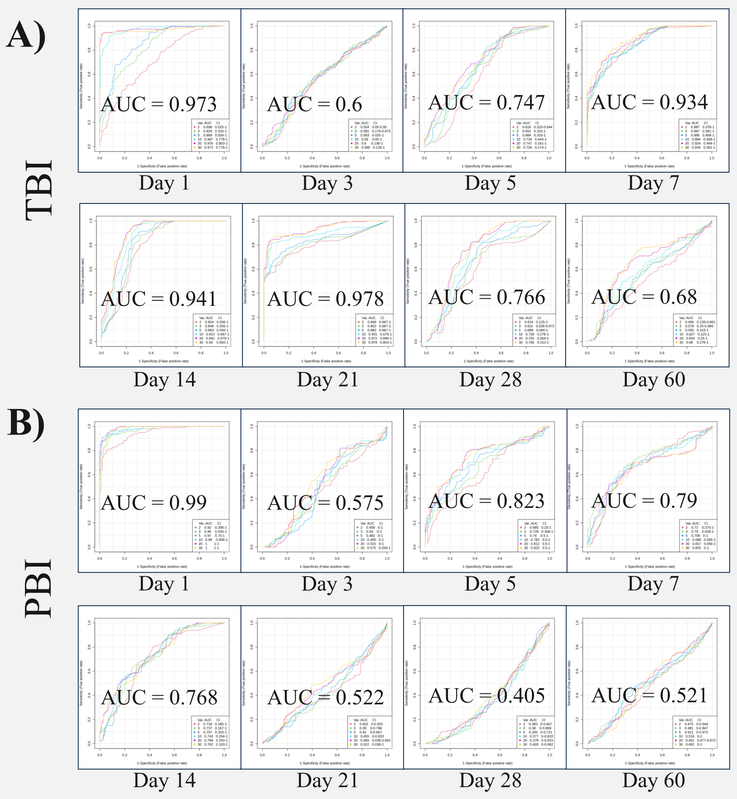


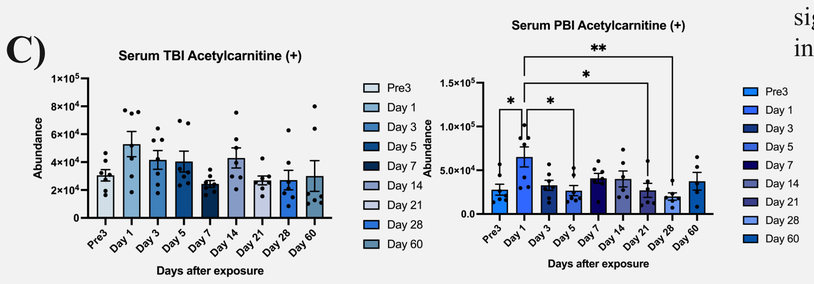
Figure 2: A) TBI and **B)** PBI ROC curves of urine metabolic response throughout 60-day post-irradiation period. ROC curves built using pre-determined TBI biomarkers. **C)** List of all urine TBI markers sourced from literature and applied to both cohorts. **D)** Bar graph comparison of 4-Pyridoxicate (-) and **E)** xanthurenate (+) abundances up to one week post-irradiation. All abundances normalized. Results reflect primarily kidney response to radiation type and shielding.

Conclusions

- Urinary metabolic response is to be expected following both TBI and PBI. Comparative analysis suggests altered kidney physiology due to PBI shielding effects.
- PBI and bone marrow shielded models are reinforced as results indicate strong hematopoietic effect of acute radiation syndrome. Further hematology analysis is required.
- Analysis is ongoing and will consider additional classifications like sex, weight, age, etc. to discern relationships. Results will better elucidate differences in NHP metabolic responses to PBI and TBI.

Serum





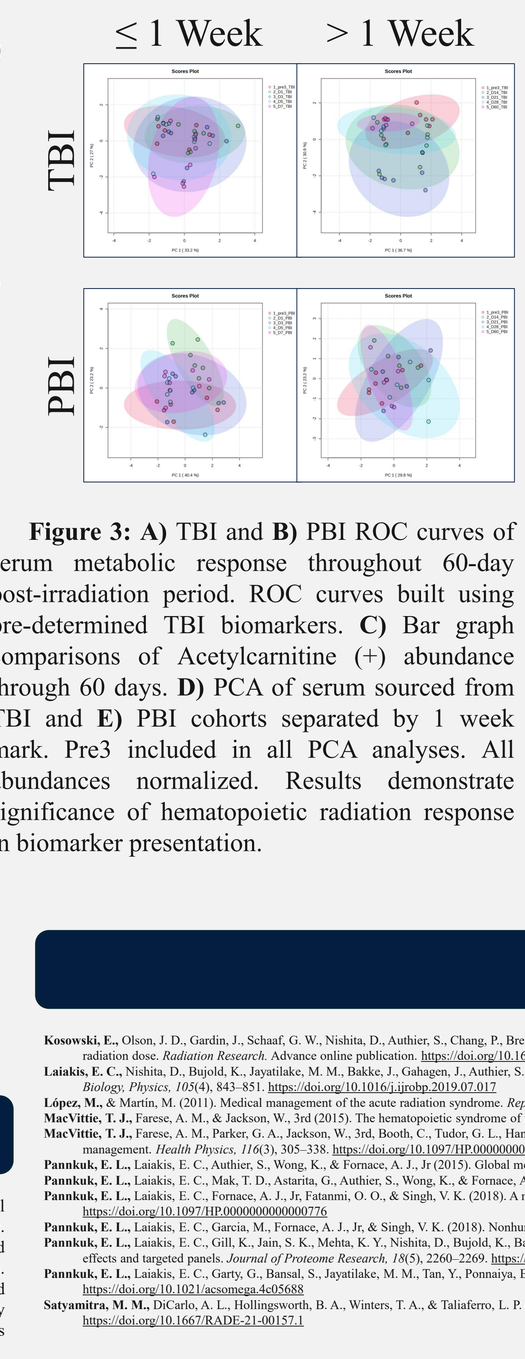


Figure 3: A) TBI and **B)** PBI ROC curves of serum metabolic response throughout 60-day post-irradiation period. ROC curves built using pre-determined TBI biomarkers. **C)** Bar graph comparisons of Acetylcarnitine (+) abundance through 60 days. **D)** PCA of serum sourced from TBI and **E)** PBI cohorts separated by 1 week mark. Pre3 included in all PCA analyses. All abundances normalized. Results demonstrate significance of hematopoietic radiation response in biomarker presentation.

Saliva

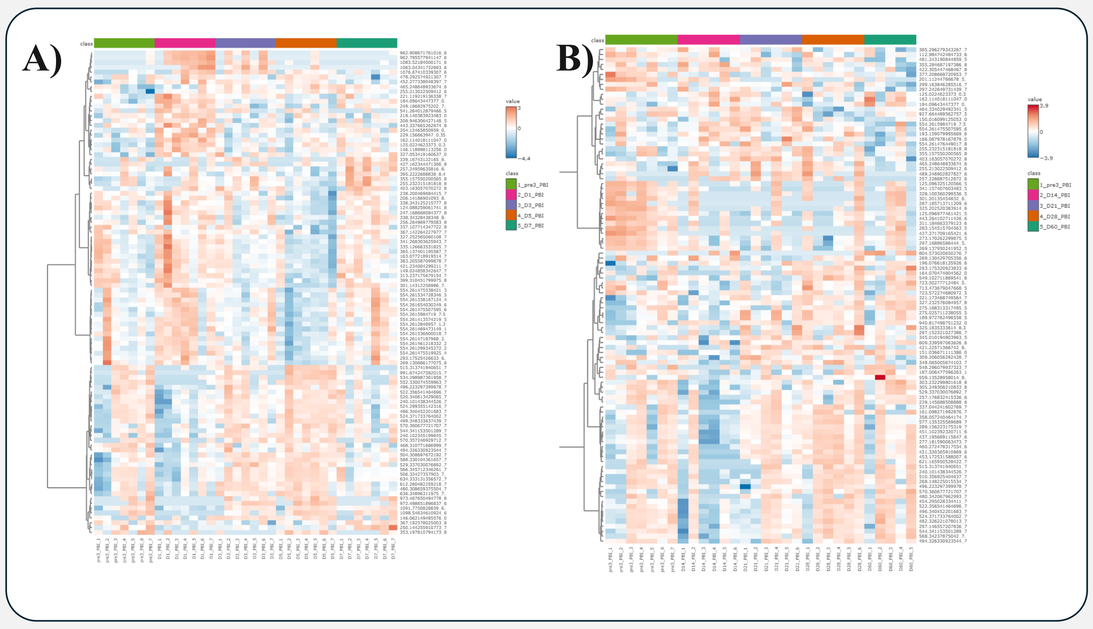


Figure 4: A) Untargeted heatmaps featuring top 100 (+) and (-) measurements for times ≤ 1 week and B) > 1 week. Both heatmaps include pre-irradiation samples. Heatmaps depict changes in ion abundances for each cohort compared to day 3 pre-irradiation. All abundances normalized. Future analysis is necessary to create PBI biomarkers from untargeted LC-MS data.

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