# SUPPLEMENTARY APPENDIX

## $F^{18}$-FDG PET imaging as a diagnostic tool for immune checkpoint inhibitor-associated acute kidney injury

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## SUPPLEMENTAL METHODS

### Adjudication of AKI Etiology in Control Patients

Two onconephrologists specializing in the care of patients with cancer and kidney-related issues independently reviewed each of the charts of patients with AKI from non-ICI causes and adjudicated the primary etiology of AKI. They were blinded to the premise of the study, but were specifically asked to comment on their clinical suspicion for ATIN. In the event of a disagreement, a third adjudicator served as a tie-breaker.

### Sex as a Biological Variable

Both males and females were involved in the study. Sex was not considered as a biological variable.

### Sensitivity Analysis

We conducted a sensitivity analysis similar to the primary analysis except that we excluded patients from the "AKI from non-ICI etiology" control group if they were receiving any of the following medications that are known to cause ATIN, at the time of AKI: non-steroidal anti-inflammatory drugs; trimethoprim-sulfamethoxazole; beta lactam antibiotics; cephalosporin antibiotics; or fluoroquinolone antibiotics.

### Statistical Analysis

We calculated an average percent change in $SUV_{mean}$ from baseline to follow-up for each patient. The Kruskal-Wallis test was used to compare the change in $SUV_{mean}$ among the three groups. A receiver operating characteristic curve was generated to evaluate the accuracy of percent change in $SUV_{mean}$ as an indicator of ICI-AKI. Analyses were performed using R version 3.6.3 (R Foundation). All P-values are two-sided, with $P<0.05$ considered statistically significant.

### Study Approval

The study was approved with a waiver of informed consent by the institutional review board at each participating site, and by the Mass General Brigham Institutional Review Board for the overall study.

### Data Availability

Data from this multicenter study are not publicly available due to contractual restrictions by the participating sites.

**Table S1: Criteria for ICI-AKI**

| **AKI that was directly attributed to the ICI by the treating provider AND either of the following criteria:** |
|---|
| **Criteria 1:** Increase in SCr ≥ 100% from baseline OR treatment with KRT |
| **Criteria 2:** Increase in SCr ≥50% from baseline AND at least one of the following:<br>1) ATIN on biopsy<br>2) ICI held for at least one cycle due to concern for ICI-AKI<br>3) Treatment with glucocorticoids due to concern for ICI-AKI |

Abbreviations: AKI, acute kidney injury; ATIN, acute tubulointerstitial nephritis; ICI, immune checkpoint inhibitor; KRT, kidney replacement therapy; SCr, serum creatinine.

**Table S2. Baseline Characteristics**

| Variable | ICI-AKI (*n*=9) | AKI from non-ICI causes (n=24) | ICI without AKI (n=20) |
|---|---|---|---|
| Age at treatment initiation, yrs, median (IQR) | 73 (60-80) | 65 (60-74) | 67 (61-74) |
| Male, n (%) | 6 (67) | 15 (63) | 15 (75) |
| Race, n (%) | | | |
| White | 8 (89) | 20 (83) | 20 (100) |
| Black | 0 (0) | 1 (4) | 0 (0) |
| Other/Unknown | 1 (11) | 3 (13) | 0 (0) |
| Comorbidities, n (%) | | | |
| Hypertension | 3 (33) | 13 (54) | 10 50) |
| Diabetes | 0 (0) | 4 (17) | 5 (25) |
| CHF | 0 (0) | 2 (8) | 0 (0) |
| COPD | 1 (11) | 0 (0) | 1 (5) |
| Cirrhosis | 0 (0) | 0 (0) | 0 (0) |
| Body mass index, median (IQR) | 23 (21-28) | 27 (24-33) | 32 (29-36) |
| Baseline eGFR,[a] ml/min per 1.73 m | | | |
| Median (IQR) | 87 (64-101) | 61 (60-91) | 79 (63-90) |
| eGFR Categories, n (%) | | | |
| ≥90 | 4 (44) | 6 (25) | 5 (25) |
| 60-89 | 4 (44) | 13 (54) | 14 (70) |
| 45-59 | 0 (0) | 5 (21) | 1 (5) |
| <45 | 1 (11) | 0 (0) | 0 (0) |
| AKI Stage,[b] n (%) | | | |
| Stage 1 | 2 (22) | 2 (8) | NA |
| Stage 2 | 1 (11) | 14 (58) | NA |
| Stage 3 | 6 (67) | 8 (33) | NA |
| Malignancy, n (%) | | | |
| Lung | 3 (33) | 0 (0) | 0 (0) |
| Melanoma | 4 (44) | 0 (0) | 14 (70) |
| Lymphoma | 2 (22) | 15 (62) | 0 (0) |
| Other | 0 (0) | 9 (38) | 6 (30) |

Data are shown as median (IQR) and n (%). Abbreviations: ICI, immune checkpoint inhibitor; AKI, acute kidney injury; IQR, interquartile range; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; mg/dl, milligram per deciliter; mCi, millicurie; PET-CT, positron emission tomography-computed tomography scan.

[a]Baseline eGFR was defined based on the SCr value closest and prior to ICI initiation, and was calculated based on Chronic Kidney Disease-Epidemiology Collaboration equation without race (1).
[b]AKI was staged according to the Kidney Disease: Improving Global Outcomes criteria (2).

**Table S3: Characteristics of PET-CT scan**

| Variable | ICI-AKI (*n*=9) | AKI from non-ICI causes (n=24) | ICI without AKI (n=20) |
|---|---|---|---|
| Blood glucose, mg/dl, median (IQR) | | | |
| Baseline PET-CT scan | 95 (86-99) | 102 (92-109) | 98 (88-115) |
| Follow-up PET-CT scan | 91 (86-108) | 102 (93-106) | 99 (90-121) |
| Radiotracer dose, mCi, median (IQR) | | | |
| Baseline PET-CT scan | 11.7 (9.1-15.9) | 14.4 (9.9-15.1) | 14.9 (9.9-20.0) |
| Follow-up PET-CT scan | 10.0 (7.9-13.6) | 11.0 (10.0-14.9) | 10.3 (9.9-19.9) |
| Uptake time, min, median (IQR) | | | |
| Baseline PET-CT scan | 61 (59-81) | 64 (59-68) | 62 (56-72) |
| Follow-up PET-CT scan | 70 (64-75) | 59 (54-69) | 69 (58-74) |
| $SUV_{mean}$, median (IQR) | | | |
| Baseline PET-CT scan | 1.8 (1.6-2.4) | 2.1 (1.9-2.5) | 2.3 (2.0-2.5) |
| Follow-up PET-CT scan | 3.2 (2.5-4.3) | 2.2 (2.0-2.6) | 2.1 (1.9-2,4) |

Data are shown as median (IQR) and n (%). Abbreviations: IQR, interquartile range; mg/dl, milligram per deciliter; mCi, millicurie; PET-CT, positron emission tomography-computed tomography scan.

**Table S4: Detailed Characteristics of ICI-AKI Patients**

| Pt # | Age/ Sex | Malignancy | ICI | SCr (mg/dl) BL / Peak / Nadir[a] | Proteinuria (dipstick/ UPCR) | LE / Blood (dipstick) | Extra-renal irAE | $SUV_{mean}$ BL / ICI-AKI (% change) |
|---|---|---|---|---|---|---|---|---|
| 1 | 75/F | Non-Hodgkin lymphoma | Nivo | 0.80/4.5/0.9 | 3+/0.74 | neg/neg | None | 1.6/5.2 (228.4) |
| 2 | 58/F | Lung adeno | Pem | 0.6/2.9/0.6 | neg/0.35 | 3+/neg | None | 1.5/3.3 (132.6) |
| 3 | 82/M | Lung adeno | Durv | 1.8/5.9/2.5 | neg/1.15 | 2+/1+ | Pneumonitis | 2.3/4.7 (107.0) |
| 4 | 56/F | Melanoma | Ipi and Nivo | 0.7/4.8/1.0 | neg/0.33 | 1+/1+ | None | 1.9/3.0 (59.0) |
| 5 | 73/M | Melanoma | Ipi and Nivo | 0.9/2.0/1.0 | neg/NA | neg/1+ | Pneumonitis | 1.5/2.3 (57.4) |
| 6 | 78/M | Hodgkin lymphoma | Nivo | 0.9/8.4/0.8 | 2+/NA | 3+/neg | None | 2.8/4.2 (53.1) |
| 7 | 61/M | Melanoma | Ipi and Nivo | 1.1/1.9/1.5 | neg/0.10 | neg/neg | Thyroiditis and pneumonitis | 1.7/2.4 (41.4) |
| 8 | 71/M | Lung SCC | Pem | 1.2/9.1/1.9 | 1+/0.64 | 3+/neg | Colitis | 1.7/2.4 (39.1) |
| 9 | 85/M | Melanoma | Pem | 1.3/2.3/1.7 | NA | NA/NA | Arthritis | 2.3/2.8 (22.1) |

Abbreviations: adeno, adenocarcinoma; AKI, acute kidney injury; BL, baseline; Durv, Durvalumab; ICI, immune checkpoint inhibitor; Ipi, Ipilimumab; irAE, immune-related adverse event; mg/dl, milligram per deciliter; LE, leukocyte esterase; NA, not available; Nivo, Nivolumab; Pem, Pembrolizumab; SCC, squamous cell carcinoma; SCr, serum creatinine; SUV, standardized uptake value; UPCR, urine protein creatinine ratio.

[a]Nadir refers to the lowest serum creatinine value achieved within 90 days following AKI onset.

**Table S5: Clinical Features of ICI-AKI Patients**

| Pt # | Biopsy-proven ATIN? | # Weeks between ICI initiation and AKI | Risk factors/clinical features of ICI-AKI | | | | Plausible alternative cause of AKI? | Treated with GC? | Kidney recovery with GC?[d] | % change in $SUV_{mean}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Combination ICI therapy?[a] | Concurrent PPI use? [b] | Prior or concomitant extrarenal irAEs? | Pyuria?[c] | | | | |
| 1 | Yes | 19 | No | No | No | No | No | Yes | Yes | 228.4 |
| 2 | Yes | 43 | No | No | No | Yes | No | Yes | Yes | 132.6 |
| 3 | Yes | 9 | No | No | Yes | NA | No | Yes | Yes | 107.0 |
| 4 | No | 28 | Yes | Yes | No | No | No | Yes | Yes | 59.0 |
| 5 | No | 11 | Yes | Yes | Yes | No | No | Yes | Yes | 57.4 |
| 6 | No | 17 | No | No | No | Yes | No | Yes | Yes | 53.1 |
| 7 | No | 10 | Yes | No | Yes | NA | No | Yes | Yes | 41.4 |
| 8 | No | 20 | No | No | Yes | Yes | No | Yes | Yes | 35.7 |
| 9 | No | 14 | No | Yes | Yes | NA | No | Yes | Yes | 22.1 |

Abbreviations: AKI, acute kidney injury; ATIN, acute tubulointerstitial nephritis; GC, glucocorticoids; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; NA, not available; PPI, proton pump inhibitor; SCr, serum creatinine; SUV, standardized uptake value.

[a]Refers to simultaneous treatment with a CTLA-4 inhibitor and a PD-1 or PD-L1 inhibitor, as this has been shown to be a risk factor for ICI-AKI (3).
[b]Concurrent PPI use has been shown to be a risk factor for ICI-AKI (4).
[c]Pyuria was defined as ≥10 WBCs per high power field.
[d]Kidney recovery was defined as a return of SCr to within 50% of baseline within 90 days of ICI-AKI. Baseline SCr was defined as the closest SCr prior to ICI initiation.

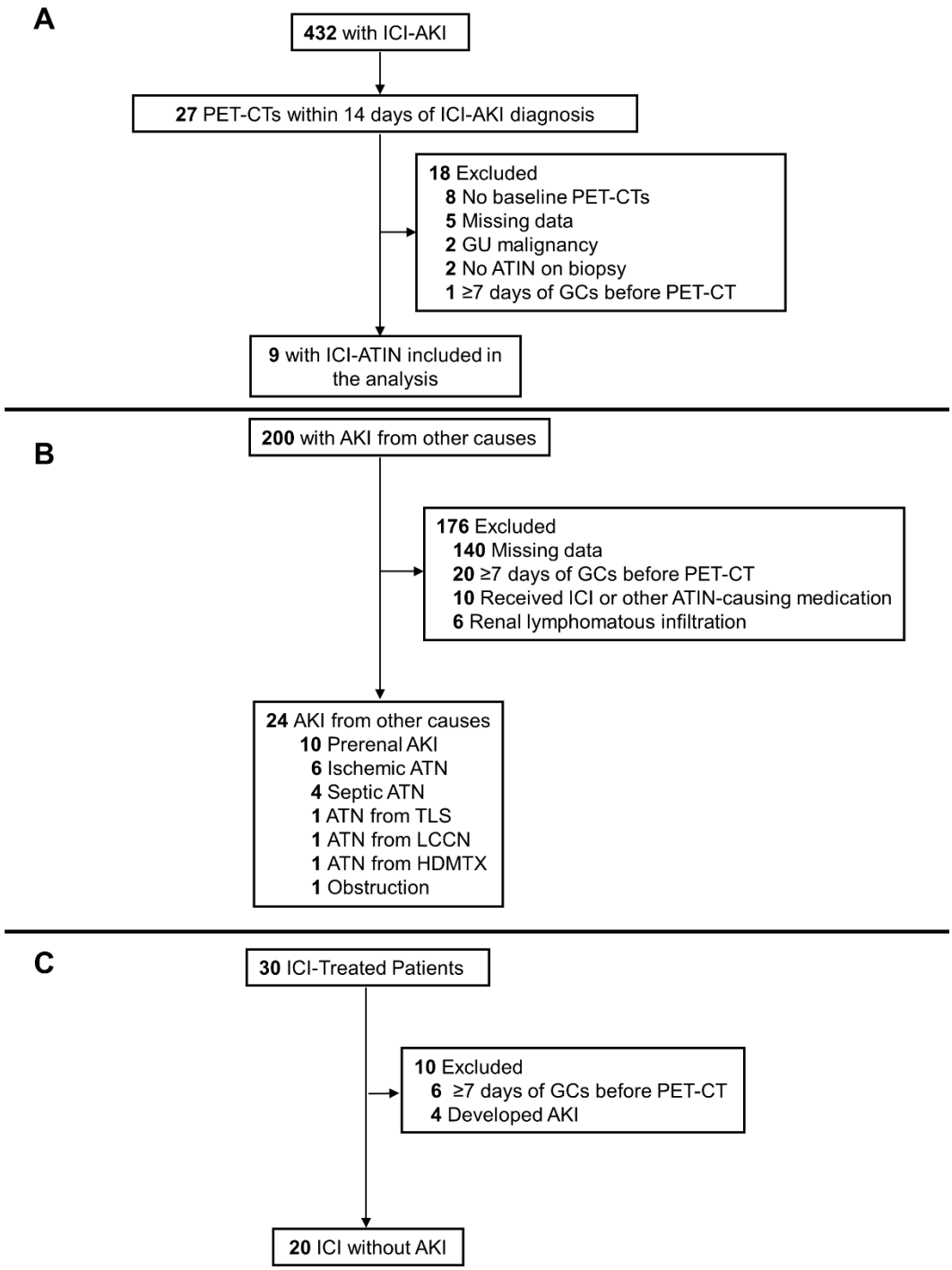
## Table S6: Clinical Features of Patients with AKI from non-ICI Etiologies

| Pt # | Age/ Sex | Malignancy | Concomittant Medications | | | $SUV_{mean}$ BL / AKI (% change) | Etiology of AKI / Clinical Setting |
|---|---|---|---|---|---|---|---|
| | | | NSAIDs | PPIs | Antibiotics | | |
| 1 | 50/F | Anal SCC | No | No | No | 2.8/2.2 (-16.1) | Prerenal: had high ostomy output; AKI responded to IVF. |
| 2 | 62/F | Mantle cell lymphoma | No | No | TMP/SMX | 2.0/2.0 (5.9) | Prerenal: resolved with supportive care; was on TMP/SMX and acyclovir but no suspicion for ATIN. |
| 3 | 71/F | Breast cancer | Yes | No | No | 2.1/2.3 (11.0) | Prerenal: was taking NSAIDs, poor PO intake, and AKI improved quickly after IVF. |
| 4 | 61/F | Endometrial | No | No | No | 2.1/2.5 (14.5) | Ischemic ATN from poor PO intake superimposed on oxalate nephropathy (biopsy-proven). |
| 5 | 67/F | DLBCL | No | Yes | Meropenem | 1.9/2.1 (15.0) | ATN from sepsis due to candidemia and enterococcal bacteremia. Low suspicion for ATIN from meropenem. |
| 6 | 74/M | Multiple myeloma | No | Yes | TMP/SMX | 2.2/2.5 (15.7) | ATN from light chain cast nephropathy, hypovolemia, and hypercalcemia. Had been on TMP/SMX and PPI for ~5 years. |
| 7 | 55/M | Multiple myeloma | No | Yes | TMP/SMX | 2.8/3.2 (21.3) | Prerenal: poor PO intake from mucositis, pneumonia. On PPI for ~7 years. |
| 8 | 78/F | Waldenstrom's macroglobulinemia | No | Yes | Amoxicillin | 1.9/2.4 (25.7) | ATN and glomerular hypoperfusion on kidney biopsy, without evidence of ATIN. |
| 9 | 60/M | Oropharyngeal SCC | No | No | No | 2.8/2.8 (11.3) | Prerenal: IV contrast and poor PO intake on a background of diabetic kidney disease. AKI improved with supportive care. |
| 10 | 84/M | DLBCL | No | No | No | 1.8/1.9 (3.8) | Hydronephrosis, with AKI improving with resolution of obstruction. |
| 11 | 61/M | PTLD | No | Yes | Vancomycin | 2.2/2.2 (1.6) | Prerenal AKI from CNI toxicity (tacrolimus) and febrile neutropenia. Had received vancomycin and cefepime a few days prior but low suspicion for ATIN. Had been on a PPI for ~ 6 years. |
| 12 | 74/M | DLBCL | No | Yes | Vancomycin Cefepime Tobramycin Metronidazole | 2.0/2.0 (4.2) | ATN secondary to septic shock and neutropenic fever. |
| 13 | 61/F | Non-Hodgkin's lymphoma | No | Yes | TMP/SMX | 3.1/3.1 (-0.4) | Prerenal: diarrhea, poor PO intake; improved with IVF. Had been on omeprazole for >3 years. |
| 14 | 72/M | DLBCL | No | No | Vancomycin Cefepime Metronidazole | 2.5/1.8 (-26.6) | ATN from septic shock and cardiogenic shock. |
| 15 | 50/M | DLBCL | No | Yes | Cefepime | 2.4/3.0 (25.4) | Ischemic ATN in the setting of cytokine release syndrome from CAR-T with third spacing. No suspicion for ATIN from PPI or cefepime. |
| 16 | 64/M | DLBCL | No | No | Levofloxacin Ceftazadime | 1.9/1.9 (0.4) | Prerenal: hypercalcemia, concomitant infection. On TMP/SMX prophylaxis but no suspicion for ATIN. |
| 17 | 76/M | CLL | No | No | Ciprofloxacin Amoxicillin | 1.9/1.9 (-4.2) | Ischemic ATN from severe hypovolemia in the setting of hypercalcemia, poor PO intake, lisinopril. Received antibiotics for a UTI after AKI episode. |
| 18 | 27/M | DLBCL | No | No | Ciprofloxacin | 1.9/2.2 (14.8) | Prerenal: improved with IVF. Had also received carboplatin and ifosfamide 7 days prior, but toxic ATN seemed less likely. |
| 19 | 78/M | DLBCL | No | No | No | 1.6/2.2 (48.7) | ATN from TLS in the setting of lymphoma. |
| 20 | 42/F | DLBCL | No | Yes | TMP/SMX | 2.0/2.7 (26.3) | Ischemic ATN in the setting of acute blood loss requiring multiple transfusions. On TMP/SMX prophylaxis but no suspicion for ATIN. |
| 21 | 67/M | DLBCL | No | No | Ceftazadime Levofloxacin | 2.3/2.0 (-15.2) | Sepsis-associated ATN in the setting of neutropenic fever. |
| 22 | 77/F | CNS lymphoma | No | Yes | No | 2.3/2.2 (-1.7) | Toxic ATN: HDMTX received 5 days prior to AKI onset. Had been on a PPI, but no suspicion for ATIN. |
| 23 | 62/M | DLBCL | No | No | Ceftriaxone | 1.3/2.0 (55.0) | Prerenal: poor PO intake, influenza, hypotension. Improved with IVF. |
| 24 | 66/M | DLBCL | No | Yes | Cephalexin | 2.6/2.0 (-24.3) | Ischemic ATN from cardiorenal syndrome, acute blood loss. Had been on a PPI for >10 years, no suspicion for ATIN. |

Patients #4 and #8 were biopsy-proven, and the remainder were clinically-adjudicated.

Abbreviations: AKI, acute kidney injury; ATN, acute tubular necrosis; ATIN, acute tubulointerstitial nephritis; BL, baseline; CAR-T, chimeric antigen receptor T-cell therapy; CLL, chronic lymphocytic leukemia; CNI, calcineurin inhibitor; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; HDMTX, high-dose methotrexate; IVF, intravenous fluids; NA, not applicable; NSAID, non-steroidal anti-inflammatory drug; PO, per os (oral); PPI, proton pump inhibitor; PTLD, post-transplant lymphoproliferative disorder; TMP/SMX, trimethoprim-sulfamethoxazole; SCC, squamous cell carcinoma; SCr, serum creatinine; SUV, standardized uptake value; TLS, tumor lysis syndrome; UTI, urinary tract infection.

**Figure S1. Flowchart of Inclusion**




Abbreviations: AKI, acute kidney injury; ATIN, acute tubulointerstitial nephritis; GC, glucocorticoids; GU, genitourinary; HDMTX, high-dose methotrexate; ICI, immune checkpoint inhibitor; LCCN, light chain cast nephropathy; PET-CT, positron emission tomography/computed tomography; TLS, tumor lysis syndrome. The 432 patients with ICI-AKI in panel A were derived from our parent publication (N=429) along with 3 additional patients identified since its publication (4).

**Figure S2. Change in $SUV_{mean}$ based on Causes of AKI**

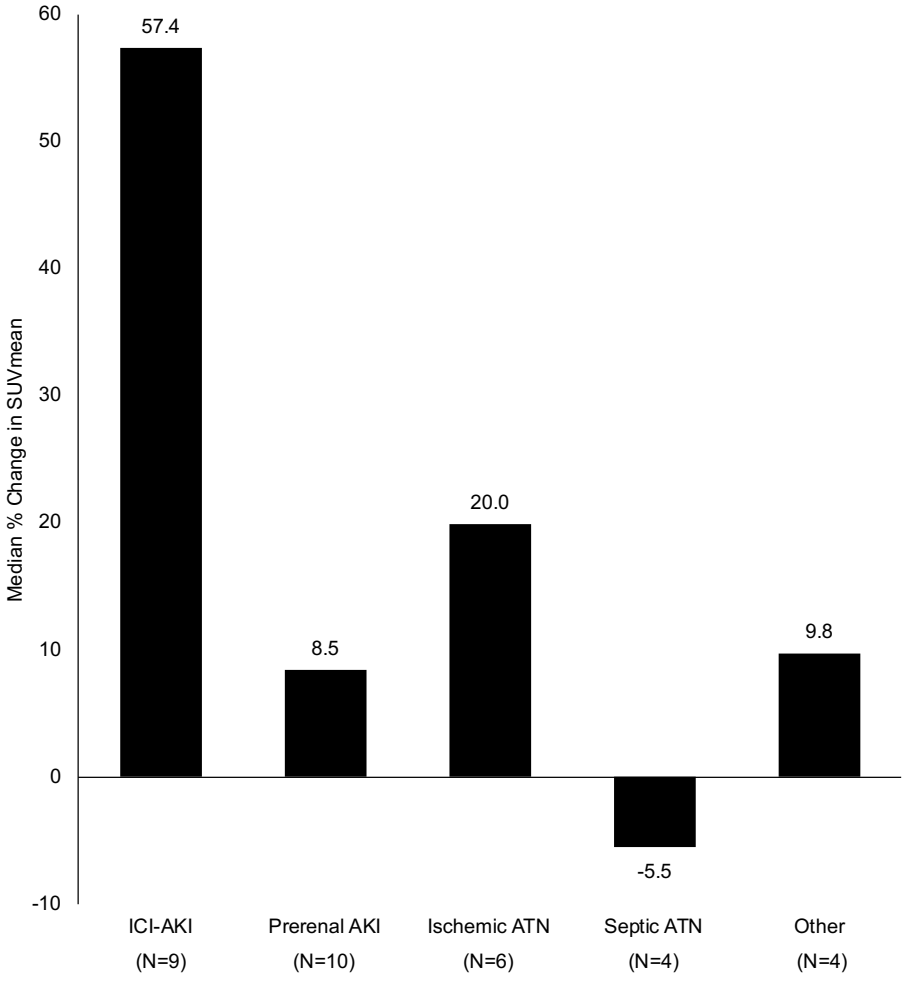


**Figure S3. ROIs at Baseline and at ICI-AKI**

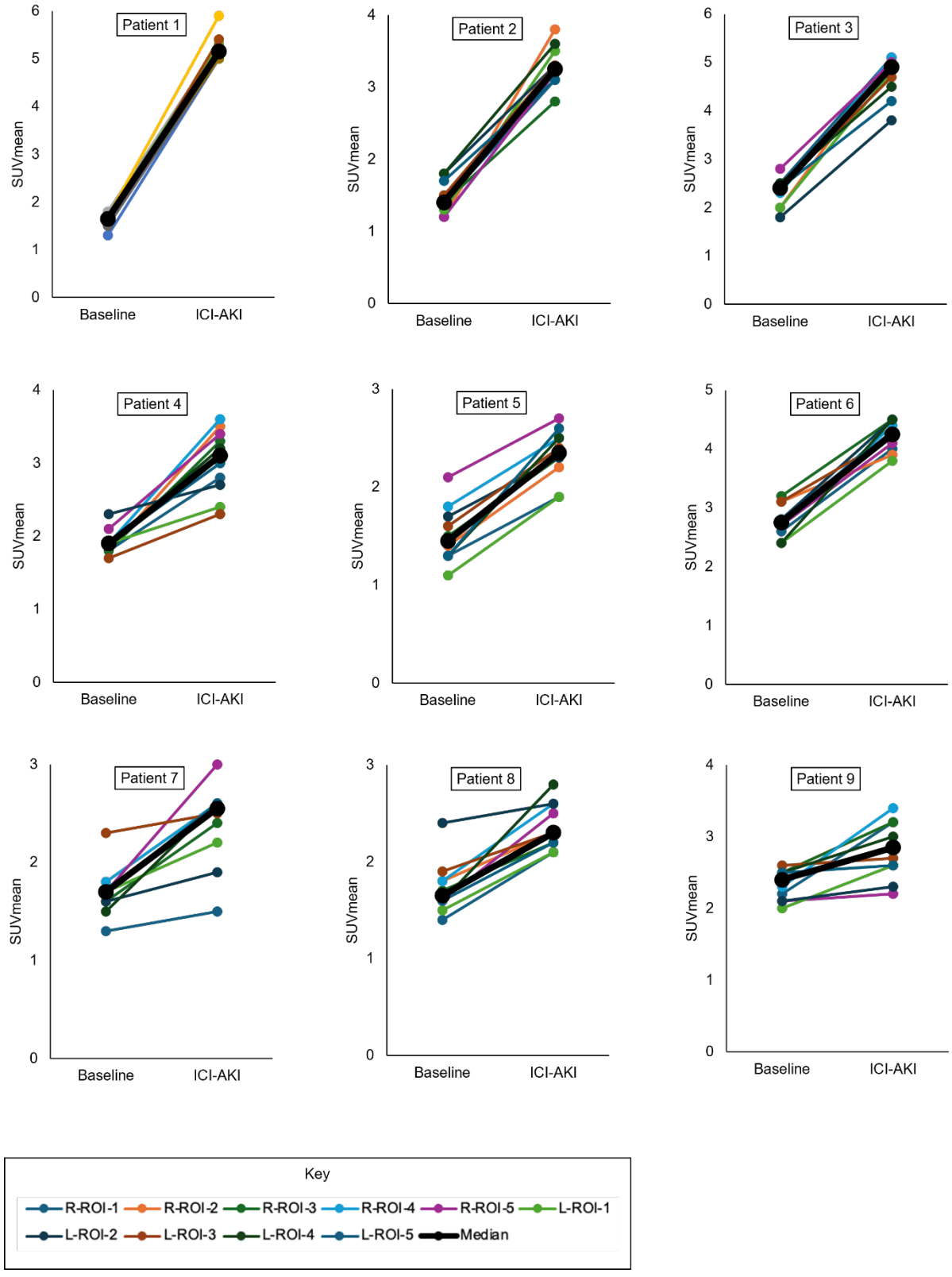
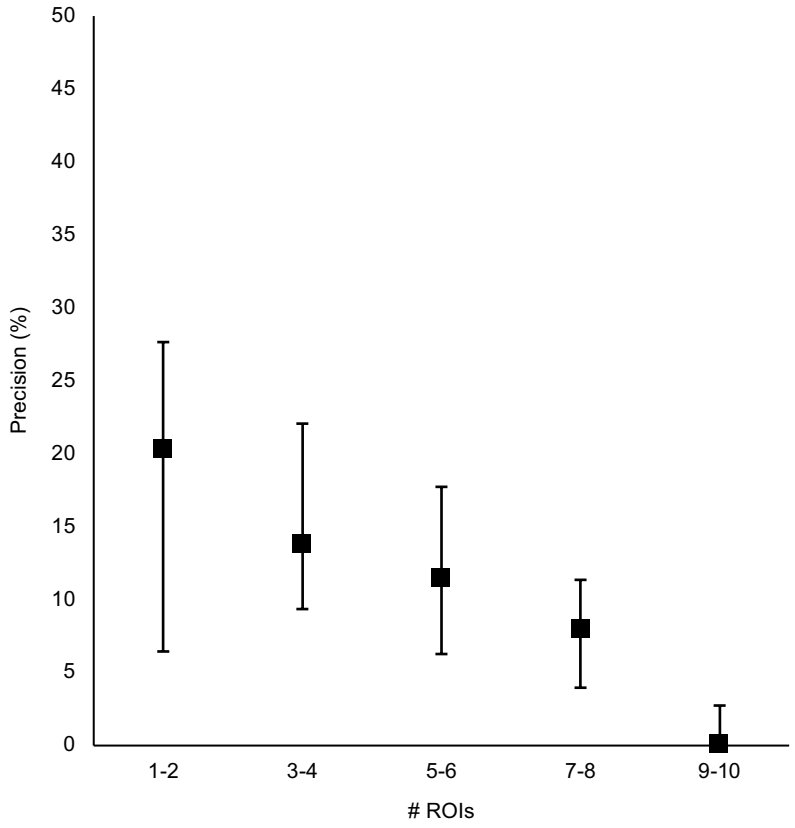


**Figure S4. Precision According to Number of ROIs of Interest**




Precision was calculated according to the number of regions of interest (ROIs) as follows: the average change in $SUV_{mean}$ for each patient was calculated according to the number of ROIs (1-2, 3-4, 5-6, 7-8, or 9-10) and compared to the overall $SUV_{mean}$ based on all 10 ROIs. The % difference from the overall $SUV_{mean}$ was calculated for each patient. The median (IQR) % difference was then assessed globally (across all 9 patients) according to number of ROIs (1-2, 3-4, 5-6, 7-8, or 9-10). Precision improved monotonically with a greater number of ROIs.

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None

**AUTHORS' CONTRIBUTIONS**
SG, OGL, and DEL designed the study, analyzed the data, and wrote the manuscript. SB analyzed all PET-CTs from patients in the two control groups. All other authors assisted with data collection, analysis, and in critically reviewing and revising the manuscript.

**DATA SHARING STATEMENT**
The authors are unable to share the raw data publicly. The Coordinating Center at Mass General Brigham has a separate data use agreement (DUA) with each of the other institutions that contributed data to the study. Each DUA has its own specifications to comply with local IRB policies from each of the contributing sites regarding sharing of data. The DUAs do not give the investigators permission to make the data publicly available in any form (with or without identifiers).

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