PHASE REPORT
IN VIVO EVALUATION OF THE EFFECTS OF THS2.2 ON THE RESPIRATORY AND CARDIOVASCULAR SYSTEMS OF APO LIPOPROTEIN E-DEFICIENT MICE

HISTOPATHOLOGY OF PANCREAS AND KIDNEY
(STUDY NUMBER 15015)

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1 Review and Approval

1.1 Study Pathologist's Statement of Compliance

The Study Pathologist acknowledges responsibility for the validity of the data.

Name	Justification	Date / Signature
Bera, Monali	Signed as Study Pathologist	31 Dec 2014 Monali Bera

2 Abstract

The purpose of this study was to characterize the effect of conventional cigarette smoke (3R4F) or THS2.2 RRP aerosol on the natural progression of renal and pancreatic disease in the Apolipoprotein E-deficient ($ApoE^{-/-}$) mouse model, following 6 and 8 months of repeated exposure. In addition, the localized effects of cessation (2 months 3R4F exposure followed by fresh air) and switching (2 months 3R4F exposure followed by exposure to THS2.2) in the kidney and pancreas were also microscopically characterized.

Mice were whole-body exposed to fresh, conditioned air or to the aerosol generated from either the reference item - mainstream cigarette smoke of the reference cigarette 3R4F at concentration of 600 µg TPM/l or to test item - aerosol from THS2.2 (matched to nicotine levels relative to 3R4F), 3 hours per day, 5 days/week for 6 and 8 months.

Animals were euthanized and the kidneys and pancreas were removed and fixed in 4% paraformaldehyde. Histoprocessing and staining of the pancreas and kidney were performed according to PMIRL-S internal working instructions. 4-µm thick, HE- stained sections of left kidney (longitudinal cut surface), and right kidney (transverse cut surface), and pancreas (longitudinal-horizontal cut surface) from 99 animals were microscopically evaluated; 49 from month 6 dissection time point and 50 from month 8 dissection time point.

The histopathological evaluation of slides was performed in a blinded manner such that knowledge of treatment groups was kept confidential by the study director to ensure that the evaluation was unbiased.

$ApoE^{-/-}$, sham control animals developed spontaneous disease conditions including: glomerular disease, pancreatic islet cell atrophy, exocrine acinar cell atrophy, hyperplasia of pancreatic ducts, and peri-pancreatic duct. Overall, these spontaneous findings in $ApoE^{-/-}$ sham controls were considered a progressive, age-related inherent background change.

In the kidney, glomerular basement membrane thickening was significantly reduced in 3R4F_6m in comparison to sham_6m and THS2.2_6m. All other groups had similar results at month 6. By month 8 all experimental groups, including 3R4F had comparable findings. Mesangial matrix expansion and glomerulosclerosis were reduced in 3R4F_6m in comparison to the other experimental groups. When comparing all experimental groups, the overall severity score assigned was in the biological range of minimal to mild. Furthermore, any differences were considered to be negligible. However, by month 8, glomerular findings in the 3R4F exposed animals were comparable to sham control group as well as the other experimental groups including cessation and switching.

In the pancreas, at month 6, THS2.2, cessation, and switching had reduced to no observed incidence of exocrine acinar cell atrophy in comparison to sham and to 3R4F. Pancreatic duct related findings were decreased in the 3R4F exposed animals in comparison to all other experimental groups for both time points, with a statistically significant difference at month 6 from THS2.2, involving ductal hyperplasia.

The majority of pancreatic parameters evaluated were similar between experimental groups, with the exception of endocrine cell (Islets of Langerhans) atrophy, where a subtle reduction in incidence was observed in THS2.2, switching, and 3R4F groups. A nicotine-related effect cannot be ruled-out entirely for this difference.

3 Introduction

See study plan.

4 Objectives

For this experimental phase, HE-stained sections of pancreas and kidney were microscopically evaluated in a blinded manner to investigate localized effects of THS2.2 as compared to 3R4F- and sham-exposed control groups following exposure for 6 and 8 months and to also assess the local effects of switching from conventional cigarettes (2 months exposure to 3R4F) to THS2.2 compared to cessation (2 months cigarette smoke followed by fresh air).

For this experimental phase, HE-stained sections of pancreas and kidney were microscopically evaluated in a blinded manner to investigate localized effects of ZRH (THS2.2) as compared to 3R4F- and sham-exposed control groups following exposure for 6 and 8 months and to also assess the local effects of switching from conventional cigarettes (2 months exposure to 3R4F) to ZRH (THS2.2) compared to cessation (2 months cigarette smoke followed by fresh air).

5 Materials and Methods

5.1 Animal model

Female ApoE$^{-/-}$ mice (TC-ApoE-F) bred under specific pathogen-free conditions were purchased from Taconic Biosciences (United Kingdom). Mice were 6-8 weeks old upon arrival and were house in an AVA accredited animal facility. Mice received gamma-irradiated pellet diet and filtered bottled tap water ad-libitum. Following a 2-week acclimatization period, mice were allocated to 10 different experimental groups (n=10/group) outlined in table 1.

Mice were whole-body exposed to fresh, condition air or to the aerosol generated from either the test or reference item: cigarette mainstream smoke of the reference cigarette 3R4F at concentrations of 600 µg TPM/l or to aerosol from THS2.2 to matched nicotine levels (relative to 3R4F), 3 hours per day, 5 days/week for 6 and 8 months. Prior to dissection, mice were for exposed for at least two consecutive days and were not fasted.

Table 1. Experimental groups

Group Code	Number of mice per group	TPM Concentration (µg/l)	Short Name
106	9	Fresh air only	Sham_6m
108	10		Sham_8m
206	10	600 µg/l	3R4F_6m
208	10		3R4F_8m
306	10	Nicotine equivalent (THS2.2)	THS2.2_6m
308	10		THS2.2_8m
406	10	600 µg/l 3R4F 2months Then fresh air	Cessation_6m
408	10		Cessation_8m
506	10	600 µg/l 3R4F for 2 months Then nicotine Equivalent (THS2.2)	Switching_6m
508	10		Switching_8m

5.2 Organ recovery and tissue staining

Non-fasted mice, were anesthetized with pentobarbital followed by blood collection through the retro-orbital plexus. Mice were perfused with 0.9% NaCl and sacrificed for organ collection. The tail of the pancreas was dissected free from the spleen while the body and head of the pancreas was dissected from the mesenteric attachments. A small proximal transverse section of the duodenum was removed together with a majority of the pancreas still intact and immersed in freshly prepared 4% paraformaldehyde (PFA) fixative solution. The left and right kidneys were removed and longitudinally and transversely sectioned respectively following by immersion fixation in 4% PFA.

Histoprocessing and staining of the pancreas and kidney were performed according to PMIRL-S internal working instructions. In short, 4% PFA fixed organs including; left kidney, right kidney, and pancreas were routinely processed, and stained (4-µm thick sections) with hematoxylin and eosin (HE).

5.3 Histopathology

HE- stained sections of left kidney (longitudinal cut surface), right kidney (transverse cut surface), and pancreas (longitudinal-horizontal cut surface) from 99 animals were microscopically evaluated; 49 from month 6 dissection time point and 50 from month 8 dissection time point.

5.3.1 Parameters and Evaluation Methods

All samples were carefully examined using pre-defined parameters and evaluation methods to characterize treatment related toxicological changes. The evaluation of the HE-stained sections was performed in a blinded manner by a veterinary pathologist who had no knowledge of individual animal treatment groups. Coded animal numbers were used in place of the actual animal identity code.

Parameters which were chosen for evaluation were based on: current guidelines for routine toxicologic pathological assessment (Frazier et al., 2012; Greaves P, 2011; Frith CH, et al., 2002) and publications describing pathological alterations in naive ApoE$^{-/-}$ mice (Wen M, et al. 2002).

Individual parameters were evaluated based on severity or incidence. Tables 2 and 3 provide a list of the pre-defined parameters used for the evaluation of pancreas and kidney respectively.

Table 2. Pancreas. Summary of individual Parameters and Evaluation Method

Compartment	**Parameter**	**Evaluation Method**
Interstitium	Fibrosis	Score
Interstitium	Infiltrate, mononuclear cells	Score
Interstitium	Inflammation, mixed cell	Score
Exocrine	Degeneration, acinar cell	Score
Exocrine	Atrophy, acinar cell	Incidence
Exocrine	Hyperplasia, ductal	Incidence
Exocrine	Fibrosis, periductal	Incidence
Endocrine (Islets of Langerhans	Vacuolation	Score
Endocrine (Islets of Langerhans	Infiltrate, mononuclear cells	Incidence
Endocrine (Islets of Langerhans	Atrophy	Incidence
Endocrine (Islets of Langerhans	hemangiectasis	Score

Table 3. Kidney. Summary of individual Parameters and Evaluation Method.

Compartment	Parameter	Evaluation Method
Interstitium	fibrosis	Score
Interstitium	infiltrate, mononuclear cell	Score
Interstitium	Inflammation, mixed cell	Score
Interstitium	Inflammation, necrotizing/suppurative	Score
Medulla	Necrosis, papilla	Score
Medulla	Pyelonephritis	Incidence
Medulla	pyelitis	Score
Vascular Changes	Congestion	Incidence
Vascular Changes	Hemorrhage	Incidence
Vascular Changes	Thrombosis, renal artery	Incidence
Glomerular Changes	Mesangial matrix expansion	Score
Glomerular Changes	Thickening, basement membrane	Incidence
Glomerular Changes	Microaneurysms	Incidence
Glomerular Changes	Mesangiolysis	Incidence
Glomerular Changes	Sclerosis, glomeruli	Score
Glomerular Changes	Sclerosis, arterioles	Incidence
Degenerative and Regenerative Changes	Casts, tubular	Incidence
Degenerative and Regenerative Changes	Atrophy/degeneration, tubular	Score

5.3.2 Criteria for Individual Scoring Systems

A scoring system was used to provide more informative, meaningful data sets to facilitate comparison between groups for selected parameters. A routine score system was used for the majority of the parameters for both kidney and pancreas. For a few select parameters, a customized scoring system with specific criteria was used for the evaluation.

5.3.2.1 Kidney

Assessment of parameters (incidence and scores) grouped under glomerular changes was performed by examining approximately 50 glomeruli at a magnification of x200. Criteria for both routine and customized scoring systems are described below.

Routine Score System

A routine score system was used to evaluate the following parameters; fibrosis, mononuclear cell infiltrate, mixed cell inflammation, necrotizing/suppurative inflammation, papillary necrosis, pyelitis, and tubular degeneration/atrophy (listed in table 3). Severity was scored on a scale from 0, 1, 2, 3, 4, to 5 and is based on the following criteria:

- Percentage of total renal subunit evaluated with the parameter.
    - For example; if mononuclear cell infiltrate is observed in >50% section, a score of 3 will be assigned.

Criteria for each score in a routine score system is outlined in table 4.

Table 4. Routine Score System: Criteria for Individual Scores (percentage of area in which the finding is observed)

Score	Criteria
0	not observed
1	< 25%
2	25 to 50%
3	> 50%
4	50-80%
5	>80%

Definition of Scoring Criteria for Parameters with a Customized Score System

A customized score system was used for parameters; mesangial matrix expansion and glomerular sclerosis. A description of each parameter and the criteria for each score is described below.

Mesangial matrix expansion

- Microscopically, several defining morphologic features are used to confirm mesangial matrix expansion. These characteristic features, in combination with the degree, extent, and chronicity of the changes determine the severity score. Table 5 defines the morphological criteria for each severity score.

Table 5. Criteria for scoring Mesangial matrix expansion

Score	**Criteria**
0	within normal limits
1	Mild increase in glomerular tuft cellularity
2	Mild to moderate increase in glomerular tuft cellularity and mesangium, mild diffuse thickening of glomerular basement membrane, occasional capillary loop dilation, parietal cell hyperplasia/hypertrophy
3	Criteria for score 2 and 4 observed equally
4	Diffuse glomerular basement membrane thickening, with diffuse thickening of bowman's capsule (BM), with or without adhesions between glomerular tuft and bowman's capsule
5	Diffuse glomerular basement membrane thickening, decreased mesangial cellularity, adhesions between capillary loops and between glomerular tuft and diffusely thickened bowman's capsule with large, distinctly prominent capillary loops (microaneurysmic dilatation).

Sclerosis

- Glomerular sclerosis is defined by several morphologic features. These characteristic features, in combination with the degree, extent, and chronicity of the sclerotic changes determine the severity score. Table 6 defines the morphological criteria for each severity score.

Table 6. Criteria for Scoring Glomerular Sclerosis

Score	Description of morphological features
0	Within normal limits
1	Mild diffusely increased mesangial matrix deposition and cellularity with or without parietal cell hyperplasia/hypertrophy
2	Moderate diffuse increase in mesangium with mesangial cells, increased thickening of GBM.
3	Segmental deposition of amorphous eosinopihilc material affecting < 25% of the glomerular tuft (sclerotic acellular nodules), thickening GBM
4	Criteria of score 3 and score 5 observed equally
5	Diffuse nodular accentuation of glomerular tuft, mesangiolysis, arteriolar hyalinzation, microaneurysms

5.3.2.2 Pancreas-Endocrine Parameters

Assessment of parameters (incidence and scores) grouped under endocrine was performed by examining approximately 15 islets at a magnification of x200.

Routine Score System

A routine score system was used to evaluate the following parameters; fibrosis, mononuclear cell infiltrate, mixed cell inflammation, acinar cell degeneration, and islet cell hemangiectasis (listed in table 2). Severity was scored on a scale from 0, 1, 2, 3, 4, to 5 and is based on the following criteria:

- Percentage of total pancreatic subunit evaluated with the parameter.
  - For example; if mononuclear cell infiltrate is observed in >50% section, a score of 3 will be assigned.

Criteria for each score in a routine score system is outlined in table 7.

Table 7. Routine Score System: Criteria for Individual Scores

Score	Criteria
0	not observed
1	< 25%
2	25 to 50%
3	> 50%
4	50-80%
5	>80%

Islets of Langerhans- vacuolation

- Definition: Individual scores reflect the percentage of total islets evaluated which contain vacuoles in combination with the degree of vacuolation within individual islets, and the chronicity.

Table 8. Criteria for Scoring Islets of Langerhans-vacuolation

Severity Score	Criteria
0	Normal
1	< 10%
2	10-30%
3	30-50%
4	50-80%
5	>80%

Islets of Langerhans- hemangiectasis

- Definition: Characterized by the enlargement, dilation or widening of blood filled capillaries within individual islets.
- Individual scores are determined based on a combination of the following criteria:
  - Percentage of total islets with this observation
  - Extent of capillary change within individual islets
  - Degree of local tissue degeneration or destruction.
- Score system: Routine (refer to table 7)

5.4 Statistical Analysis

The statistical analysis was conducted internally by BSR statisticians based in Neuchatel (Patrice Leroy) See section 9 for the raw data.

The following items have been reported:

a. The list of findings grouped by time point and exposure type;
b. The contingency tables by Finding, Time point, and Exposure, showing the proportion of animals that exhibit the presence of an incidence or the severity of a finding, as well as the number of observations, of missing observations and not evaluated animals.
c. A table of group means, by finding and exposure type.
d. A table of inferential statistics testing all pairwise comparisons below,
    i. Incidences have been tested using a Fisher exact test,
    ii. Scores have been tested using a Cochran-Mantel-Haenszel test on the row mean score.
e. Figures, graphically representing the contingency tables
    i. A set representing the proportion of animals, given the severity of the finding,
    ii. Another set representing the mean severity as well as the minimum and maximum severity.

6 Results

As ApoE $^{-/-}$ mice age, they naturally develop systemic pathology in various organs due to their inherent homozygous mutation. Findings observed in 6 and 8 months dissections in sham groups were considered naturally occurring background lesions. When differences from "background" were observed for any of the parameters, the observation was described further to facilitate differentiating a primary treatment-related change from naturally occurring disease.

6.1 Parameters with Significant Difference in Group Mean Results

Statistical pairwise comparison was performed between all experimental groups. Parameters between two groups with significant differences are listed ($p \leq 0.05$), with the group with the higher mean score **bolded and underlined**.

6.1.1 Kidney

- Degenerative and Regenerative Changes- atrophy/degeneration, tubular
  - 3R4F_m6 vs. **3R4F_m8**
- Interstitium- fibrosis
  - Switching_m6 vs **Switching_m8**
- Medulla- pyelitis
  - THS2.2_m6 vs. **THS2.2_m8**
- Glomerular changes- mesangial matrix expansion
  - 3R4F_m6 vs. **3R4F_m8**
- Glomerular changes- thickening, basement membrane
  - 3R4F_m6 vs. **Sham_m6**
  - 3R4F_m6 vs. **3R4F_m8**
  - 3R4F_m6 vs. **THS2.2_m6**
- Glomerular changes- sclerosis, glomeruli
  - 3R4F_m6 vs. **Sham_m6**
  - 3R4F_m6 vs. **3R4F_m8**
  - 3R4F_m6 vs. **cessation_m6**
  - 3R4F_m6 vs. **Switching_m6**

6.1.2 Pancreas

- Interstitium- infiltrate, mononuclear cells
  - 3R4F_m6 vs. **Cessation_m6**
  - 3R4F_m8 vs. **THS2.2_m8**
- Exocrine- degeneration, acinar cell
  - Switching_m6 vs **Switching_m8**
- Exocrine- atrophy, acinar cell
  - **3R4F_m6** vs THS2.2_m6
  - Switching_m6 vs **Switching_m8**
  - THS2.2_m6 vs. **THS2.2_m8**
  - **3R4F_m6** vs. Switching_m6
- Exocrine- hyperplasia, ductal
  - 3R4F_m6 vs **THS2.2_m6**
- Islets of Langerhans- vacuolation
  - **THS2.2_m6** vs. THS2.2_m8
- Islets of Langerhans- hemangiectasis
  - **3R4F_m8** vs.Sham_m8
  - **3R4F_m8** vs. THS2.2_m8
  - **3R4F_m8** vs. Cessation_m8
  - 3R4F_m6 vs. **3R4F_m8**
  - **3R4F_m8** vs. Switching_m8

6.2 Summary of Results

A summary of the histopathology results are described in the following sections for kidney and pancreas. Under each organ sub-category, the main findings in the sham groups are summarized first as this provides an overview of what is considered 'normal' in this mouse model. The descriptive summary which follows places emphasis on treatment-related findings as compared to sham (background), overall trends, and the biological relevance of statistically significant findings (section 6.1.1).

6.2.1 Kidney-Histopathology Findings

Glomerular Changes

ApoE$^{-/-}$, sham control animals developed spontaneous glomerular disease characterized by; diffuse mesangial expansion, thickened basement membrane, and glomerulosclerosis. These features are consistent with what has been previously described (Wen M, et al. 2002).

Mesangial matrix expansion was observed in all groups for both time points. In general, results were comparable for all experimental groups. The only statistically significant difference was observed in 3R4F_6m compared to 3R4F_8; the latter having a higher score. The difference was considered biologically insignificant as the severity of the finding did not increase dramatically from month 6 to month 8 and remained mild at most.

Thickening of the glomerular basement membrane was observed in all groups for both time points. Findings were similar between all experimental groups, except 3R4F_6m, where incidence was dramatically reduced in comparison to all other experimental groups. Cessation and switching groups had comparable results for both time points. By month 8, all experimental groups including 3R4F had comparable findings.

Glomerular sclerosis was significantly decreased at month 6 in 3R4F when compared to all other experimental groups, with the exception of THS2.2. The biological relevance for these results was considered negligible as the severity score was minimal at most when observed. Glomerular microaneurysms, mesangiolysis, and arteriolar sclerosis were also evaluated, however the results were disregarded. These parameters were difficult to accurately identify on the sections provided for evaluation and could be easily missed, resulting in more false negatives. Evaluation of these parameters would benefit from thinner sections and additional histochemical stains to provide more interpretative results.

Degenerative and Regenerative Changes/ Inflammatory Changes

Tubular casts were present at 100% incidence across all groups. Tubular atrophy and/or degeneration was observed in all groups including sham. All experimental groups had higher scores at month 8 than month 6. There were no treatment-related changes when compared to sham groups. Only one group was statistically significant; 3R4F_8m (increased) compared to 3R4F_6m. This result and overall trends seen in other groups, suggests a progressive tubular change. This finding was considered biologically insignificant based on the low severity score.

Inflammatory changes were observed and scored for the following parameters; infiltration of mononuclear cells, fibrosis, and pyelitis. . Pairwise comparison showed that interstitial fibrosis was significantly increased in switching_m8 compared to switching_6m. This difference was considered biologically insignificant as the increase in severity was minimal at most. Pyelitis or inflammation of the renal pelvis was significantly increased in THS2.2_8m compared to THS2.2_6m. Although a significant difference was observed, the

overall severity remained within a baseline background range. The renal pelvis is in direct communication with the ureter, and it is not uncommon to see minimal inflammatory cell infiltrates in the lamina propria subjacent to the urothelium.

Overall, the tubulointerstital subunit of the kidney in all experimental groups was well preserved with minimal mononuclear cell infiltrate, minimal interstitial fibrosis, and with little indication of tubular damage. Although, severity scores were minimal, there still remained an overall trend where findings at month 8 were increased relative to month 6. These findings were observed in all groups with no treatment-related effects when compared with sham controls.

6.2.2 Pancreas-Histopathology Findings

Interstium and Exocrine

Spontaneous findings of the exocrine pancreatic subunit in ApoE$^{-/-}$ were progressive in nature within a time period of two months, suggesting an age-related background change. The main changes included; atrophy and minimal degeneration of acinar cells, hyperplasia of pancreatic ducts, and peri-pancreatic duct fibrosis with minimal to mild mononuclear cell infiltrates. Frequency for all observations were greater at month 8.

Pancreatic acinar cell atrophy was observed in sham controls at both time points. The main differences were seen at month 6, where THS2.2, cessation, and switching had reduced to no incidence of acinar cell atrophy in comparison to sham and to 3R4F. At month 6, 3R4F had significantly increased incidence in comparison to THS2.2 and switching. By months 8, all experimental groups had comparable results.

Ductal hyperplasia and peri-ductal fibrosis were observed in all experimental groups for both time points. In general, 3R4F had reduced incidence for both parameters at both time points in comparison to all other groups. Ductal hyperplasia was significantly reduced in 3R4F_6m in comparison to THS2.2. By month 8, ductal changes in all experimental groups, excluding 3R4F, were comparable.

Endocrine (Islets of Langerhans)

Spontaneous islet cell atrophy was the main (~70% incidence) endocrine finding in ApoE$^{-/-}$ sham control groups. Incidence remained the same at month 6 and month 8. Incidence of islet cell atrophy at month 6 was reduced in 3R4F and switching when compared to sham_6m. At 8 months, islet cell atrophy increased in 3R4F whereas in switching there was no change. Islet cell atrophy was reduced in THS2.2_8m compared to THS2.2_6m. This trend was a complete reversal from what was observed in 3R4F, with atrophy increasing by month 8. Incidence following switching, was the same as THS2.2_8m where less atrophic islets were observed. There were minimal to no difference in islets cells between cessation and sham controls.

Islet cell vacuolation and hemangiectasis was observed in all groups including sham. The only statistically significant treatment related change from sham was in 3R4F_8m where hemangiectasis was increased. Pairwise comparison also showed a significant increase in 3R4F_8m when compared to THS2.2_8m,

Cessation_8m, and switching_8m. The severity score for all groups was minimal to mild, and the difference was considered biologically insignificant.

Infiltration of islets of Langerhans by mononuclear cells was evaluated at month 6 only. This finding was observed in all groups with no statistically significant differences.

6.2.2.1 Undefined findings

Undefined findings described below were observed during the course of the evaluation and recorded. Since these findings were not part of the original list of parameters, results were not processed.

Islets of Langerhans, Heptaocellular Metaplasia

Hepatocellular metaplasia was observed in the pancreas of animals at time points. Pairwise comparison or mean incidence is not available as this was an undefined finding. In the data entry sheet, this finding was evaluated as incidence.

Exocrine, Lobular Atrophy, Generalized

This finding was included to supplement the defined parameter, "acinar cell atrophy," which was evaluated as incidence. Since incidence does not provide information on the distribution or extent of the finding, generalized lobular atrophy was included to capture the over distribution and magnitude of the atrophic acini. This finding was evaluated as incidence and was not processed for statistical analysis.

7 Abbreviations and Definition of Terms

Abbreviation/Term	
ApoE$^{-/-}$	Apolipoprotein E deficient
HE	Hematoxylin and Eosin
GBM	Glomerular basement membrane
OECD	Organization for economic co-operation and development
PMIRL-S	Philip Morris International Research Laboratories- Singapore
TPM	Total particulate matter

8 References

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9 Tables and Figures

Table 9. Histopathology, listing of raw data, sham.

		Sham																			
		6m												8m							
		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		6	6	6	6	6	6	6	6	6	6	8	8	8	8	8	8	8	8	8	8
		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		1	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2
		9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8
Left Kidney																					
Degenerative and Regenerative Changes																					
casts, tubular	Incidence	P	P	P	P	P	P	P	P	-	P	P	P	P	-	P	P	P	P	P	P
atrophy/degeneration, tubular	Score	1	-	0	1	1	2	0	1	-	0	2	1	-	-	0	0	-	2	1	-
Inflammatory Changes																					
Interstitium																					
infiltrate, mononuclear cell	Score	2	1	0	1	0	0	2	0	-	0	1	1	0	-	0	1	1	1	0	-
inflammation, mixed cell	Score	0	0	0	0	0	0	0	0	-	0	0	0	0	-	0	0	0	0	0	-
fibrosis	Score	1	1	1	1	0	0	2	0	-	0	1	1	2	-	0	0	-	0	0	-
inflammation, necrotizing/suppurative	Score	3	0	0	0	0	0	0	0	-	0	0	0	0	-	0	0	0	0	0	-
Medulla																					
necrosis, papilla	Incidence	N	N	N	N	N	N	N	N	-	N	N	N	N	-	N	N	N	N	N	-
pyelonephritis	Incidence	N	N	N	N	N	N	N	N	-	N	N	N	N	-	N	N	N	N	N	-
pyelitis	Score	2	0	0	-	0	0	1	0	-	0	1	1	0	-	0	0	1	0	0	-
Vascular Changes																					
congestion	Incidence	P	P	P	P	P	P	P	P	-	P	P	P	-	-	P	P	-	P	P	-
hemorrhage	Incidence	N	N	N	N	P	N	N	N	-	N	N	N	-	-	N	N	-	N	N	-
thrombosis, renal artery	Incidence	N	N	N	N	N	N	N	N	-	N	N	N	-	-	N	N	-	N	N	-
Glomerular Changes																					
mesangial matrix expansion	Score	2	3	1	3	3	3	3	2	-	1	3	3	3	-	1	1	2	3	2	-
thickening, basement membrane	Incidence	P	P	N	P	P	P	P	P	-	N	P	P	P	-	N	N	P	P	P	-
microaneurysms	Incidence	N	N	N	P	N	N	P	N	-	N	N	N	N	-	N	N	-	P	N	-
mesangiolysis	Incidence	N	N	N	P	N	N	P	N	-	N	N	N	N	-	N	N	-	P	N	-
sclerosis, glomeruli	Score	1	0	0	2	1	2	4	0	-	0	1	1	0	-	0	0	-	2	0	-
sclerosis, arterioles	Incidence	N	N	N	N	N	N	P	N	-	N	N	N	-	-	N	N	-	N	N	-
Pancreas																					
Interstitium																					
fibrosis	Score	0	0	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0
infiltrate, mononuclear cells	Score	1	0	0	0	1	1	0	1	-	0	2	0	0	1	1	0	1	1	1	3
inflammation, mixed cell	Score	0	0	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0
Exocrine																					
degeneration, acinar cell	Score	0	0	0	1	0	1	1	1	-	2	1	0	1	1	1	0	0	1	2	1
atrophy, acinar cell	Incidence	N	N	N	N	N	P	P	N	-	P	N	P	P	P	P	N	N	P	P	N
hyperplasia, ductal	Incidence	N	N	N	N	P	P	N	P	-	N	P	N	N	P	P	N	N	P	P	P
fibrosis, periductal	Incidence	N	N	N	N	N	P	N	N	-	N	P	N	N	P	P	N	N	P	P	P
Endocrine (Islets of Langerhans)																					
vacuolation	Score	0	0	0	1	0	1	0	1	-	1	1	0	0	0	0	0	1	0	0	0
infiltrate, mononuclear cells	Incidence	P	N	N	N	P	P	N	N	-	N	-	-	-	-	-	-	-	-	-	-
atrophy	Incidence	N	P	P	P	P	P	P	N	-	P	P	N	P	P	P	N	N	P	P	P
hemangiectasis	Score	1	1	1	1	1	0	0	1	-	1	1	1	1	1	1	1	1	1	1	1

Table 10. Histopathology, listing of raw data, 3R4F.

		3R4F																			
		6m										8m									
		20019	20601	20622	20623	20624	20625	20626	20627	20628	20629	20801	20802	20803	20804	20805	20806	20807	20808	20809	20810
Left Kidney																					
Degenerative and Regenerative Changes																					
casts, tubular	Incidence	P	-	-	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
atrophy/degeneration, tubular	Score	0	-	-	0	0	1	-	0	0	1	-	1	2	-	1	2	0	1	1	1
Inflammatory Changes																					
Interstitium																					
infiltrate, mononuclear cell	Score	0	-	-	0	0	1	1	1	0	1	1	0	1	-	0	1	1	1	1	0
inflammation, mixed cell	Score	0	-	-	0	0	0	0	0	0	0	0	0	0	-	0	0	0	0	0	0
fibrosis	Score	0	-	-	0	0	1	0	0	0	1	1	0	2	-	0	1	1	0	1	0
inflammation, necrotizing/suppurative	Score	0	-	-	0	0	0	0	0	0	0	0	0	0	-	0	0	0	0	0	0
Medulla																					
necrosis, papilla	Incidence	N	N	-	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
pyelonephritis	Incidence	N	N	-	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
pyelitis	Score	0	0	-	0	0	0	1	0	0	1	0	0	0	0	1	1	0	1	1	0
Vascular Changes																					
congestion	Incidence	P	-	-	P	P	P	P	P	P	P	P	P	P	-	P	P	P	P	P	P
hemorrhage	Incidence	N	-	-	N	N	P	N	N	N	N	N	N	P	-	N	P	N	P	N	N
thrombosis, renal artery	Incidence	N	-	-	N	N	N	N	N	N	N	N	N	N	-	N	N	N	N	N	N
Glomerular Changes																					
mesangial matrix expansion	Score	1	-	-	2	2	3	2	2	1	2	3	2	3	-	3	3	3	3	3	2
thickening, basement membrane	Incidence	N	-	-	N	N	P	N	N	N	N	P	P	P	-	P	P	P	P	P	P
microaneurysms	Incidence	N	-	-	N	N	N	N	N	N	N	N	N	P	-	N	N	P	N	N	N
mesangiolysis	Incidence	N	-	-	N	N	N	N	N	N	N	N	P	-	-	N	N	N	N	P	N
sclerosis, glomeruli	Score	0	-	-	0	0	0	0	0	0	0	0	1	-	-	1	1	1	1	1	0
sclerosis, arterioles	Incidence	N	-	-	N	N	N	N	N	N	N	N	N	-	-	N	N	N	N	N	N
Pancreas																					
Interstitium																					
fibrosis	Score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
infiltrate, mononuclear cells	Score	0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	1	0	0	0	1
inflammation, mixed cell	Score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Exocrine																					
degeneration, acinar cell	Score	1	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	1	0	1	2
atrophy, acinar cell	Incidence	P	N	N	N	P	N	N	P	P	P	P	P	P	N	N	N	N	P	P	P
hyperplasia, ductal	Incidence	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	P	P	N	N	N
fibrosis, periductal	Incidence	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	P
Endocrine (Islets of Langerhans)																					
vacuolation	Score	0	0	0	0	1	0	0	1	1	1	0	0	0	0	1	1	0	1	0	1
infiltrate, mononuclear cells	Incidence	N	N	N	N	N	N	N	N	P	N	-	-	-	-	-	-	-	-	-	-
atrophy	Incidence	P	N	N	N	N	N	N	P	P	P	N	P	N	P	N	P	P	P	P	P
hemangiectasis	Score	1	1	1	1	1	1	1	1	1	1	1	1	2	1	2	1	2	1	1	2

Table 11. Histopathology, listing of raw data, THS2.2.

		THS 2.2																			
		6m										8m									
		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		6	6	6	6	6	6	6	6	6	6	8	8	8	8	8	8	8	8	8	8
		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		1	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2
		9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8
Left Kidney																					
Degenerative and Regenerative Changes																					
casts, tubular	Incidence	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
atrophy/degeneration, tubular	Score	0	2	0	0	2	1	0	1	1	0	2	0	0	2	1	1	0	-	1	-
Inflammatory Changes																					
Interstitium																					
infiltrate, mononuclear cell	Score	0	1	0	0	1	0	0	1	0	0	2	0	1	1	1	0	0	0	1	-
inflammation, mixed cell	Score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-
fibrosis	Score	0	2	0	0	1	0	0	1	0	0	2	0	1	1	1	0	0	1	1	-
inflammation, necrotizing/suppurative	Score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-
Medulla																					
necrosis, papilla	Incidence	N	N	N	N	N	N	N	N	N	N	N	-	N	N	N	N	N	N	N	
pyelonephritis	Incidence	N	N	N	N	N	N	N	N	N	N	N	-	N	N	N	N	N	N	N	
pyelitis	Score	0	1	0	0	1	0	0	0	0	0	1	0	-	1	1	0	1	1	1	1
Vascular Changes																					
congestion	Incidence	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
hemorrhage	Incidence	P	N	N	N	N	N	N	N	N	P	P	N	N	N	P	N	N	N	-	
thrombosis, renal artery	Incidence	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Glomerular Changes																					
mesangial matrix expansion	Score	1	3	2	3	3	2	2	3	2	1	3	1	3	3	3	3	1	3	2	2
thickening, basement membrane	Incidence	N	P	P	P	P	P	N	P	P	N	P	N	P	P	P	P	N	P	N	-
microaneurysms	Incidence	N	P	N	N	N	N	N	P	N	P	N	N	N	N	P	N	N	N	-	
mesangiolysis	Incidence	N	P	N	N	N	N	N	P	N	P	N	P	N	N	N	N	N	N	-	
sclerosis, glomeruli	Score	0	4	0	0	0	0	0	1	2	0	3	0	1	0	1	1	0	0	0	-
sclerosis, arterioles	Incidence	N	P	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	-
Pancreas																					
Interstitium																					
fibrosis	Score	-	0	0	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0
infiltrate, mononuclear cells	Score	-	3	1	0	0	0	0	1	3	-	2	1	0	1	2	2	0	2	0	3
inflammation, mixed cell	Score	-	0	0	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0
Exocrine																					
degeneration, acinar cell	Score	-	1	1	0	0	1	1	1	1	-	0	0	1	1	1	1	1	0	0	1
atrophy, acinar cell	Incidence	-	N	N	N	N	N	N	N	N	-	P	N	P	P	N	N	P	P	N	N
hyperplasia, ductal	Incidence	-	P	P	N	N	P	P	P	P	-	N	N	P	P	P	P	P	P	N	P
fibrosis, periductal	Incidence	-	P	N	N	N	P	P	N	N	-	N	N	N	N	N	N	P	N	N	P
Endocrine (Islets of Langerhans)																					
vacuolation	Score	-	1	1	0	0	2	1	1	1	-	0	0	0	0	2	0	0	0	0	1
infiltrate, mononuclear cells	Incidence	P	P	P	N	N	N	N	P	P	-	-	-	-	-	-	-	-	-	-	-
atrophy	Incidence	-	N	N	P	N	P	P	P	P	-	N	N	P	N	P	N	N	P	N	P
hemangiectasis	Score	-	1	1	1	1	0	1	1	1	-	1	1	0	1	1	1	1	1	1	1

Table 12. Histopathology, listing of raw data, cessation.

		Cessation																			
		6m												8m							
		4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		6	6	6	6	6	6	6	6	6	6	8	8	8	8	8	8	8	8	8	8
		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		1	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2
		9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8
Left Kidney																					
Degenerative and Regenerative Changes																					
casts, tubular	Incidence	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
atrophy/degeneration, tubular	Score	0	-	2	0	1	1	2	0	-	0	1	1	2	0	-	1	1	3	1	3
Inflammatory Changes																					
Interstitium																					
infiltrate, mononuclear cell	Score	0	1	1	0	1	1	2	0	1	1	0	0	4	1	1	1	1	1	0	1
inflammation, mixed cell	Score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
fibrosis	Score	0	-	2	0	1	1	1	0	-	0	1	0	2	0	1	1	0	2	0	2
inflammation, necrotizing/suppurative	Score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Medulla																					
necrosis, papilla	Incidence	-	N	N	N	N	N	N	N	N	N	N	N	-	N	N	N	N	N	-	N
pyelonephritis	Incidence	-	N	N	N	N	N	N	N	N	N	N	N	-	N	N	N	N	N	N	N
pyelitis	Score	-	0	1	0	1	0	0	0	1	1	1	1	-	0	1	0	0	0	-	1
Vascular Changes																					
congestion	Incidence	P	P	P	P	P	P	P	P	-	P	P	P	P	-	P	P	P	P	P	P
hemorrhage	Incidence	N	N	N	N	N	P	N	N	-	P	N	N	N	-	N	P	N	P	N	N
thrombosis, renal artery	Incidence	N	N	N	N	N	N	N	N	-	N	N	N	N	N	N	N	N	N	N	N
Glomerular Changes																					
mesangial matrix expansion	Score	1	1	3	1	3	3	3	1	2	2	3	2	3	2	3	3	3	3	2	3
thickening, basement membrane	Incidence	N	N	P	N	P	P	P	N	P	P	P	N	P	P	P	P	P	P	N	P
microaneurysms	Incidence	N	N	P	N	P	N	N	N	-	P	N	N	P	N	N	N	N	N	N	N
mesangiolysis	Incidence	N	N	P	N	N	N	P	N	-	N	N	N	N	N	N	N	N	N	N	N
sclerosis, glomeruli	Score	0	0	4	0	1	1	3	0	-	0	0	0	2	0	2	1	1	2	0	1
sclerosis, arterioles	Incidence	N	N	P	N	N	N	P	N	-	N	N	N	N	N	N	N	N	N	N	N
Pancreas																					
Interstitium																					
fibrosis	Score	0	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0
infiltrate, mononuclear cells	Score	1	0	3	0	3	1	2	-	1	0	3	1	0	3	4	0	0	2	1	0
inflammation, mixed cell	Score	0	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0
Exocrine																					
degeneration, acinar cell	Score	1	0	1	0	1	0	1	-	1	0	1	0	0	1	1	0	0	1	0	1
atrophy, acinar cell	Incidence	N	N	N	N	N	N	N	-	P	N	P	N	P	P	N	N	N	N	P	P
hyperplasia, ductal	Incidence	P	N	P	N	P	N	P	-	P	N	N	N	N	P	P	N	N	P	P	N
fibrosis, periductal	Incidence	P	N	P	N	N	N	P	-	N	N	N	P	N	P	N	N	N	P	P	N
Endocrine (Islets of Langerhans)																					
vacuolation	Score	1	0	0	0	0	1	0	-	1	0	0	1	0	1	2	0	0	0	0	0
infiltrate, mononuclear cells	Incidence	P	N	P	N	P	P	P	-	N	N	-	-	-	-	-	-	-	-	-	-
atrophy	Incidence	P	P	P	N	P	N	P	-	P	N	N	P	P	P	P	N	P	P	P	P
hemangiectasis	Score	1	0	1	1	1	0	1	-	0	1	1	1	1	1	1	1	1	1	1	0

Table 13. Histopathology, listing of raw data, switch.

		Switch																			
		6m										8m									
		5002	5006	5006	5006	5006	5006	5006	5006	5006	5006	5008	5008	5008	5008	5008	5008	5008	5008	5008	5008
		0122	0122	0122	0122	0122	0122	0122	0122	0122	0122	0122	0122	0122	0122	0122	0122	0122	0122	0122	0122
		1290	1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212	1213	1214	1215	1216	1217	1218	1219
Left Kidney																					
Degenerative and Regenerative Changes																					
casts, tubular	Incidence	P	P	-	P	P	P	P	P	P	P	P	P	P	P	P	-	P	P	P	
atrophy/degeneration, tubular	Score	-	1	-	0	1	0	0	2	0	1	-	1	1	0	2	-	-	1	2	1
Inflammatory Changes																					
Interstitium																					
infiltrate, mononuclear cell	Score	0	1	-	0	1	0	1	1	0	1	1	1	1	0	1	0	-	1	1	1
inflammation, mixed cell	Score	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0	0	-	0	0	0
fibrosis	Score	0	0	-	0	1	0	0	0	0	1	-	1	1	0	1	0	-	2	2	1
inflammation, necrotizing/suppurative	Score	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0	0	-	0	0	0
Medulla																					
necrosis, papilla	Incidence	-	N	-	N	N	N	N	N	N	N	N	N	N	N	N	N	-	N	N	N
pyelonephritis	Incidence	-	N	-	N	N	N	N	N	N	N	N	N	N	N	N	N	-	N	N	N
pyelitis	Score	3	1	-	0	0	0	1	0	0	1	0	0	0	1	0	2	-	1	1	0
Vascular Changes																					
congestion	Incidence	-	P	-	P	P	P	P	P	P	P	P	P	P	P	P	P	-	P	P	P
hemorrhage	Incidence	-	N	-	N	N	N	P	N	N	N	N	N	N	N	N	N	-	N	N	N
thrombosis, renal artery	Incidence	-	N	-	N	N	N	N	N	N	N	N	N	N	N	N	N	-	N	N	N
Glomerular Changes																					
mesangial matrix expansion	Score	-	3	-	1	3	2	2	3	2	2	1	3	3	3	3	3	-	2	3	2
thickening, basement membrane	Incidence	-	P	-	N	P	N	P	P	N	P	N	P	P	P	P	P	-	N	P	P
microaneurysms	Incidence	-	N	-	N	N	N	N	P	N	N	N	N	N	N	N	N	-	N	P	N
mesangiolysis	Incidence	-	N	-	N	N	N	N	P	N	N	N	N	N	N	N	N	-	N	P	N
sclerosis, glomeruli	Score	-	1	-	0	1	1	0	2	0	0	0	1	1	0	1	0	-	0	4	0
sclerosis, arterioles	Incidence	-	N	-	N	N	N	N	N	N	N	N	N	N	N	N	N	-	N	P	N
Pancreas																					
Interstitium																					
fibrosis	Score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
infiltrate, mononuclear cells	Score	2	0	0	3	0	0	3	1	0	0	0	0	2	1	1	0	4	2	2	1
inflammation, mixed cell	Score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Exocrine																					
degeneration, acinar cell	Score	0	0	0	1	0	1	2	0	0	0	1	2	1	1	0	0	2	1	1	2
atrophy, acinar cell	Incidence	N	N	N	N	N	N	N	N	N	N	P	P	P	P	P	P	N	P	N	N
hyperplasia, ductal	Incidence	N	N	N	N	N	P	P	N	N	N	N	N	P	P	P	N	P	P	P	P
fibrosis, periductal	Incidence	N	N	N	N	N	N	P	N	N	N	N	P	N	P	N	N	P	N	N	P
Endocrine (Islets of Langerhans)																					
vacuolation	Score	1	0	0	0	0	2	0	0	1	0	0	0	0	0	0	-	0	1	1	1
infiltrate, mononuclear cells	Incidence	P	N	N	N	N	P	P	N	N	N	-	-	-	-	-	-	-	-	-	-
atrophy	Incidence	N	N	N	P	N	N	P	N	P	P	N	N	P	N	P	-	N	P	N	P
hemangiectasis	Score	1	0	2	1	1	1	1	1	1	0	1	1	1	1	0	-	1	1	1	1

Statistics

9.1.1 Means-Maximum and Minimum

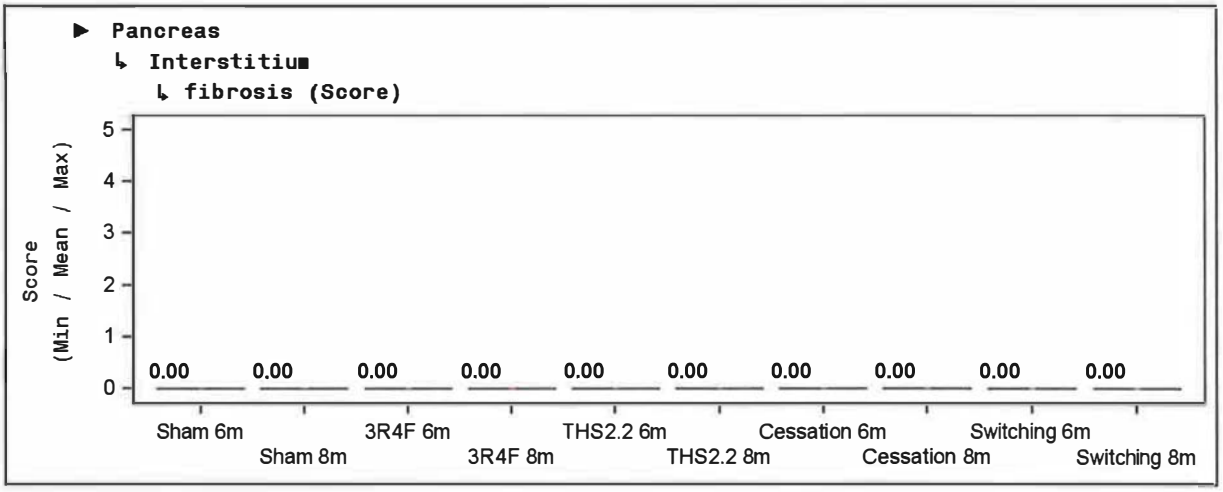


Figure 1.

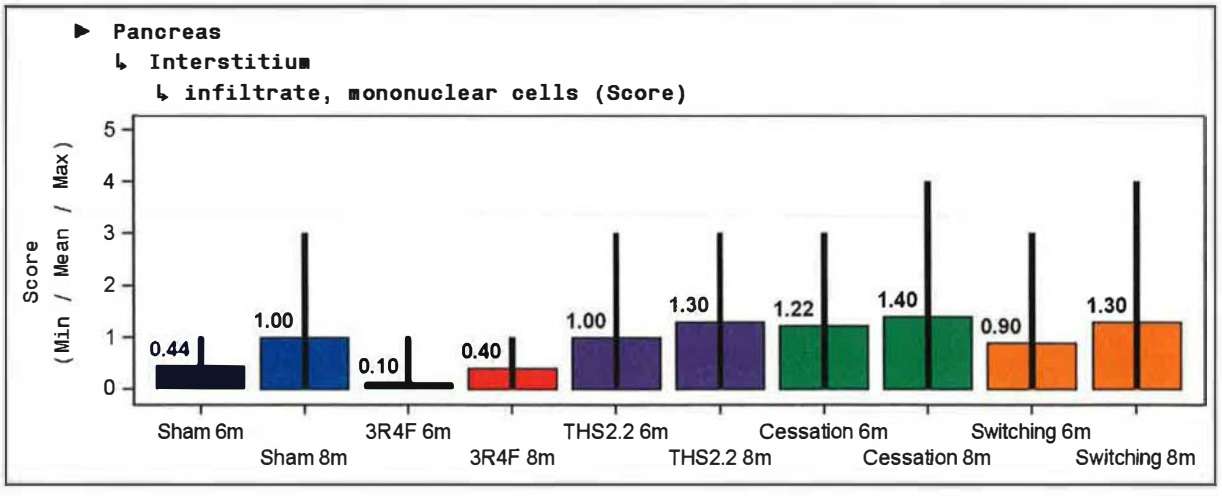


Figure 2.

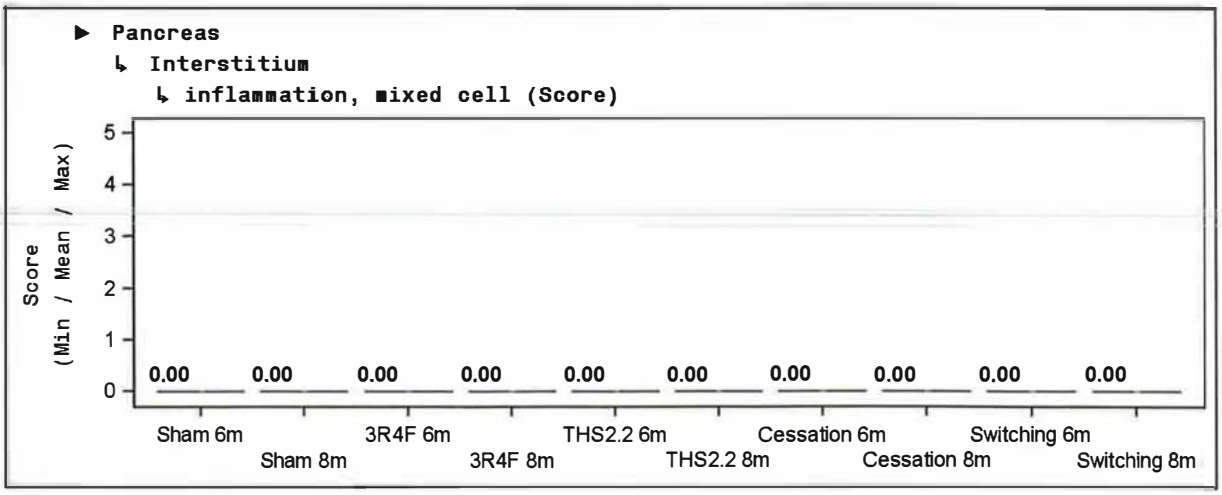


Figure 3.

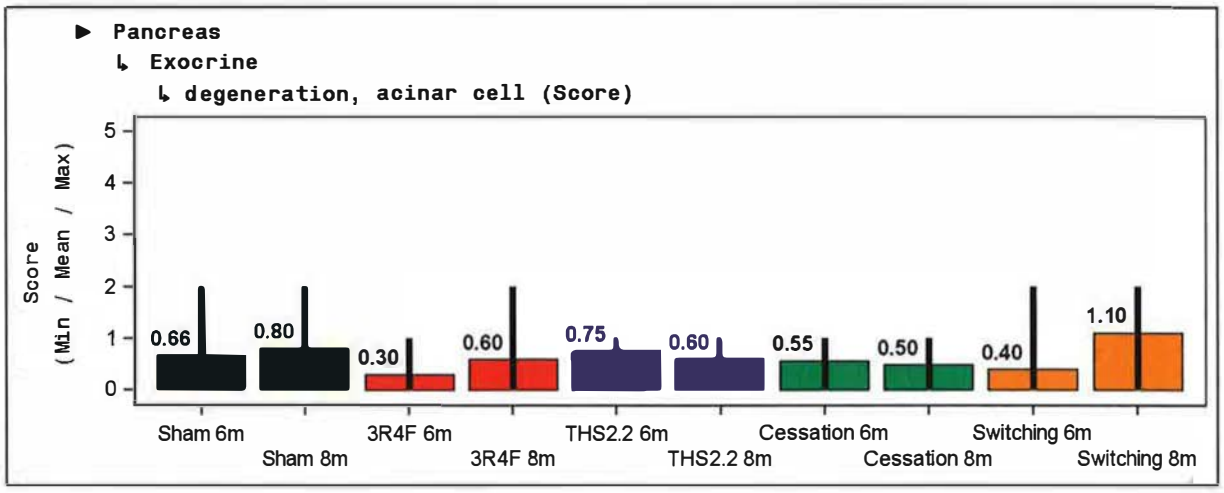


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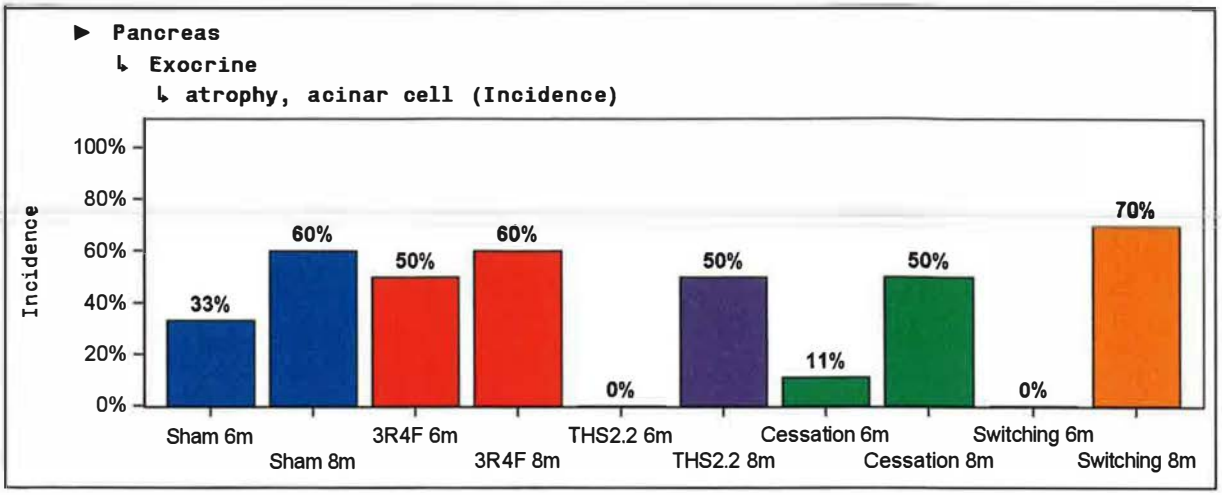


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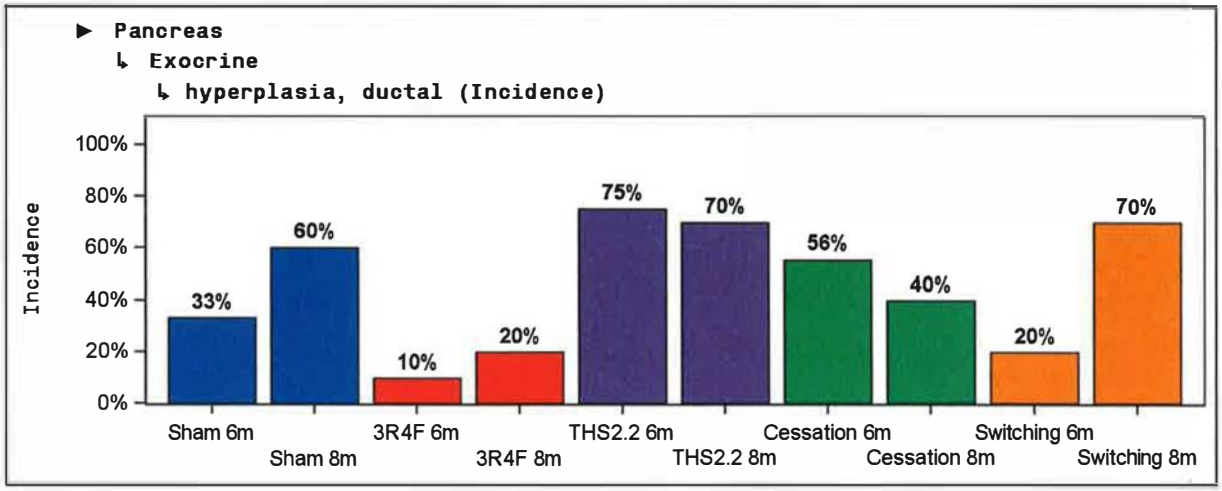


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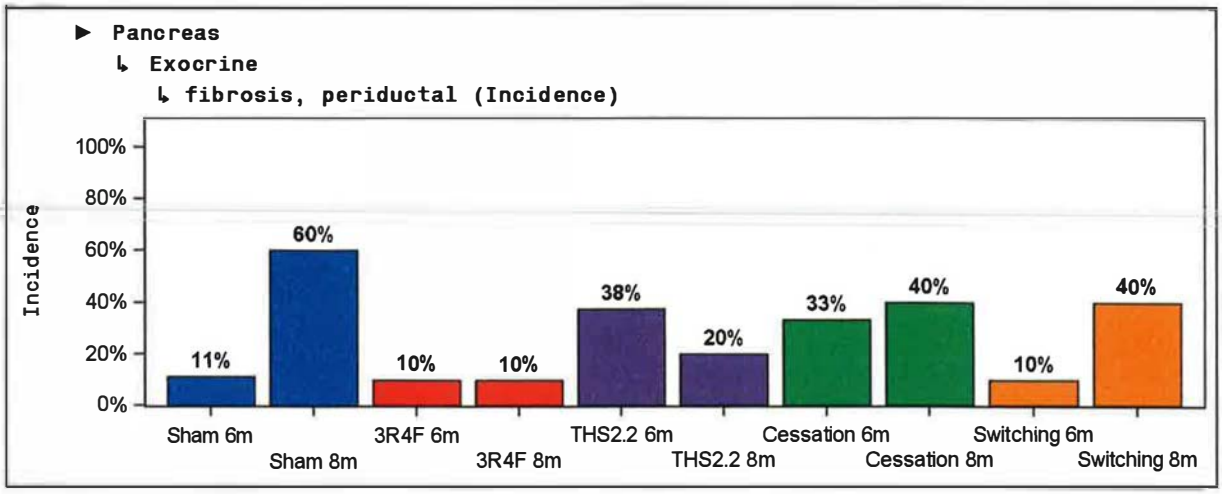


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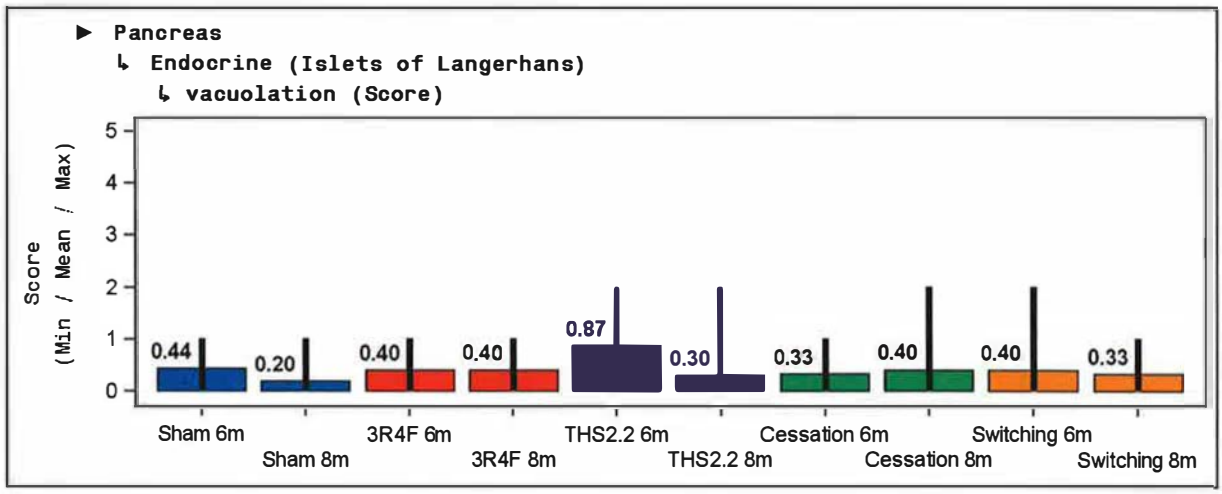


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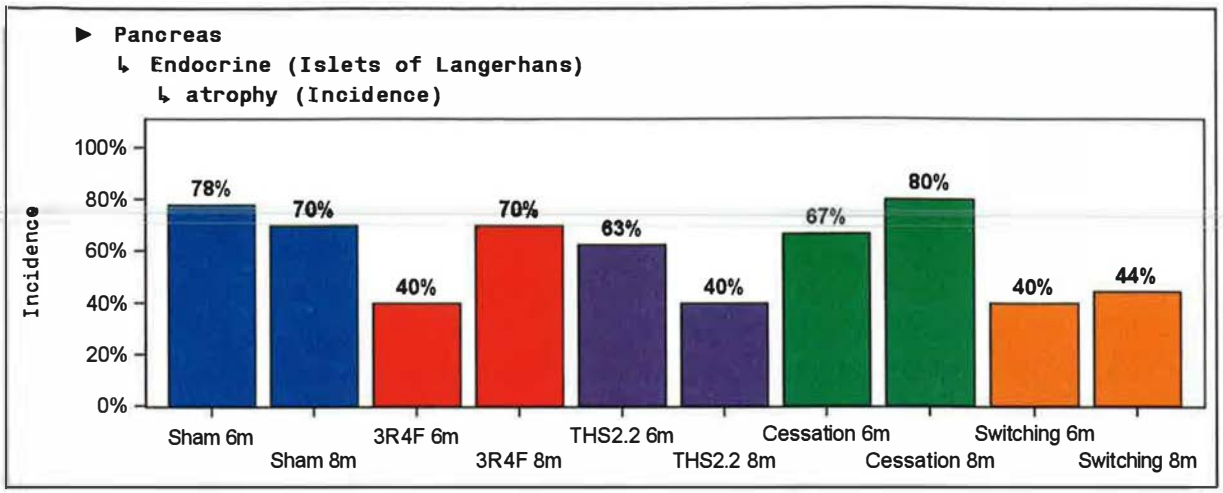


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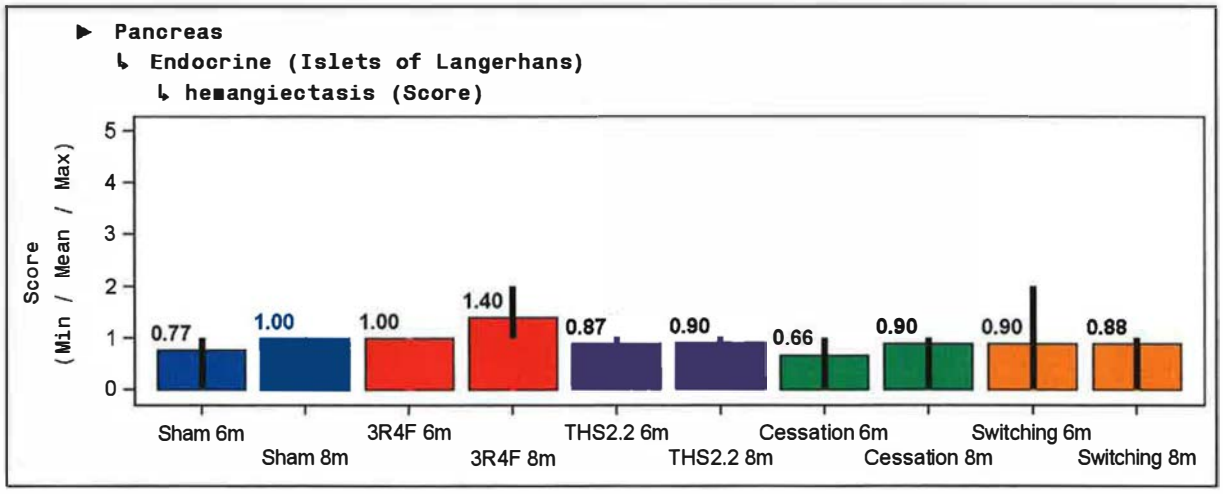


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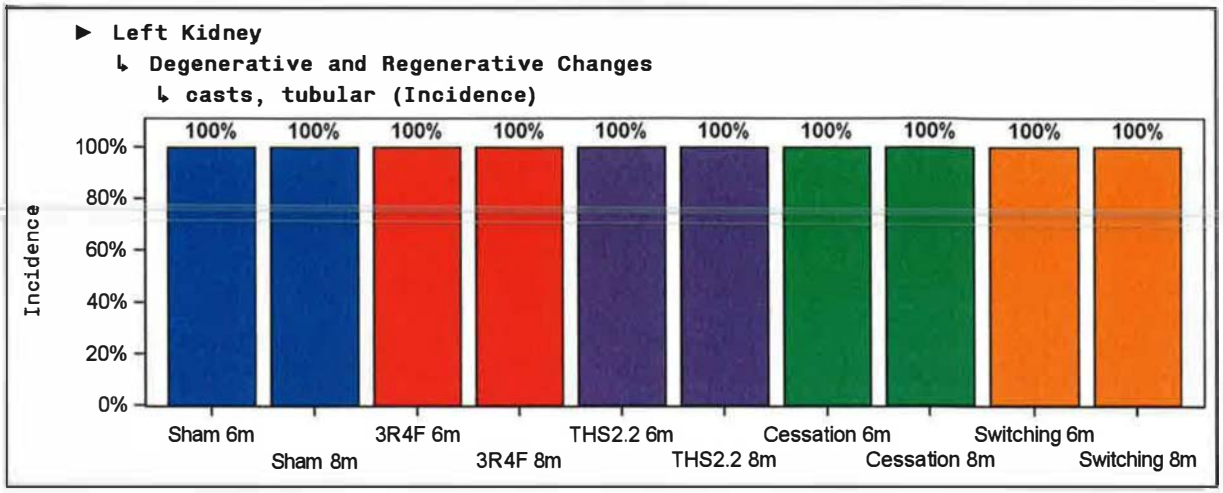


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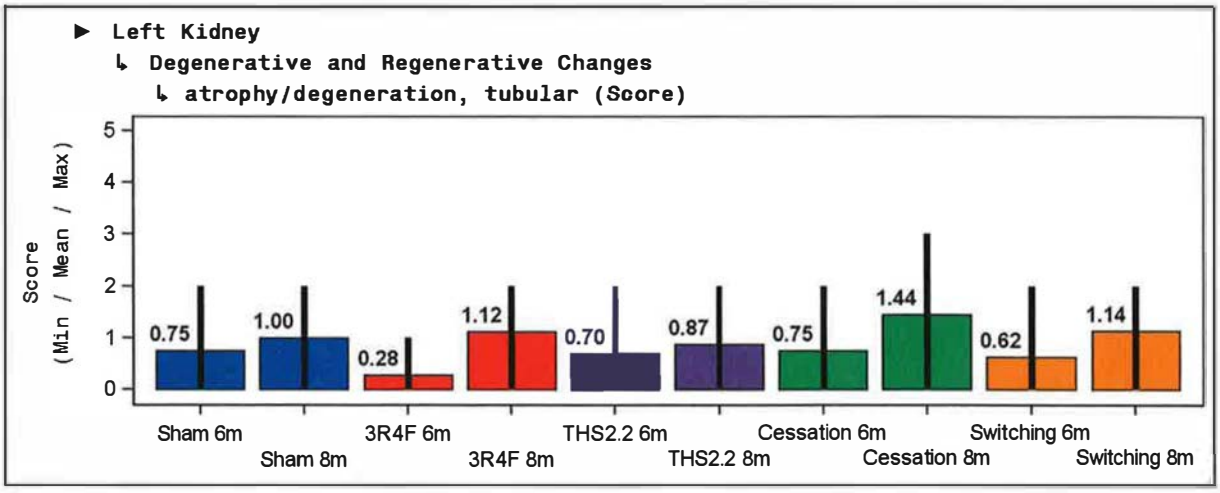


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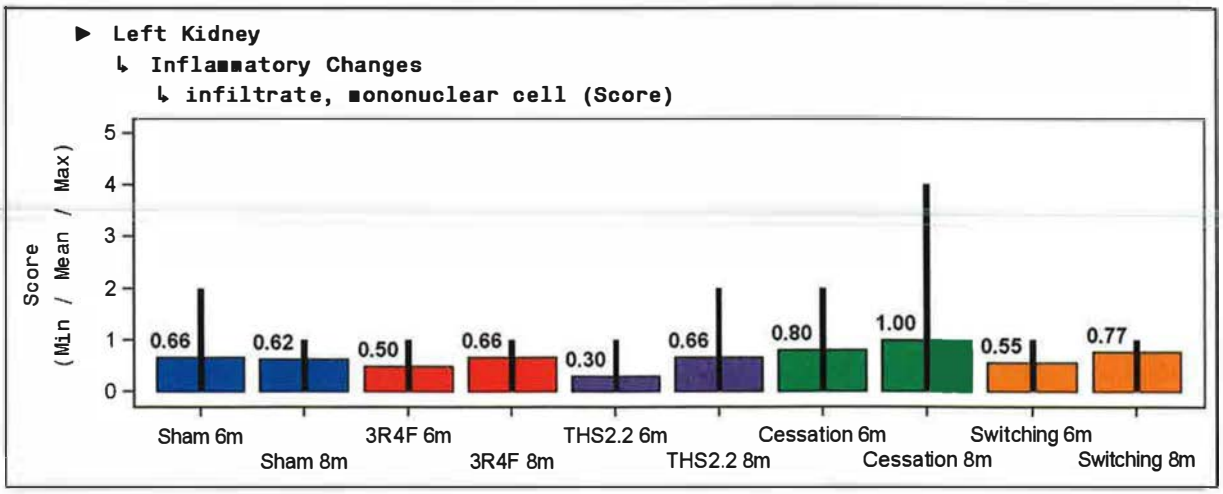


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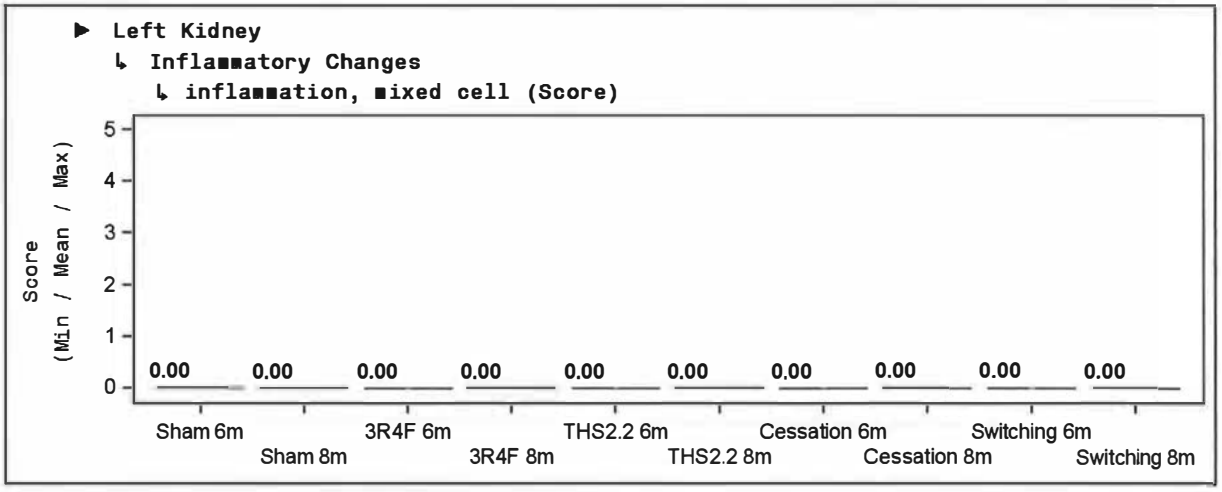


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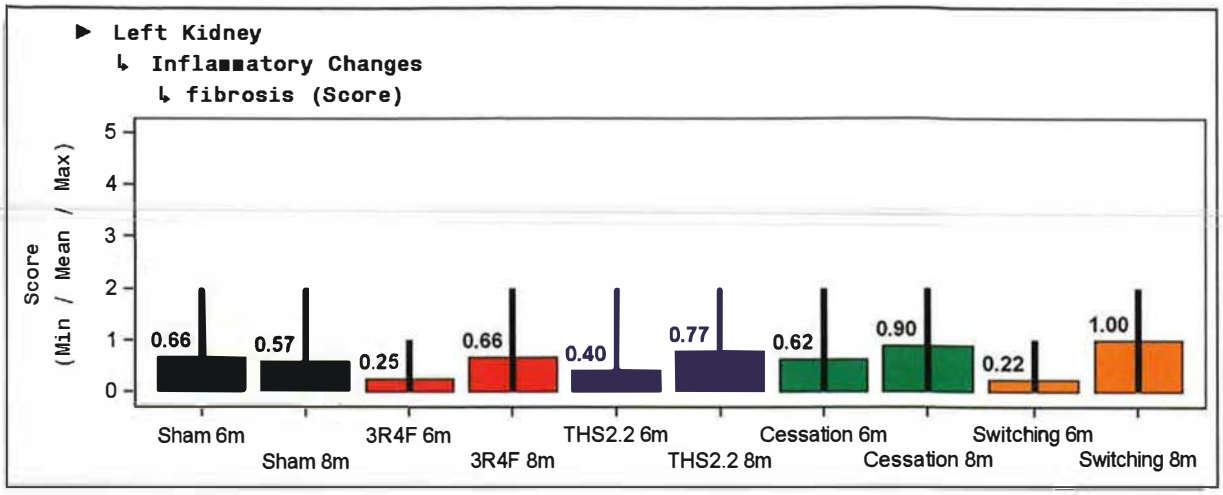


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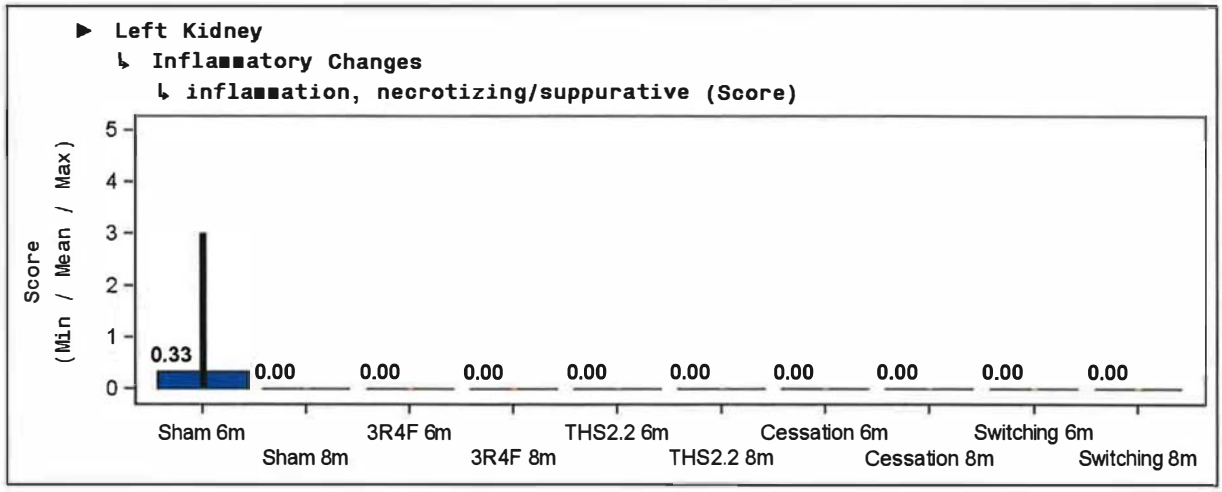


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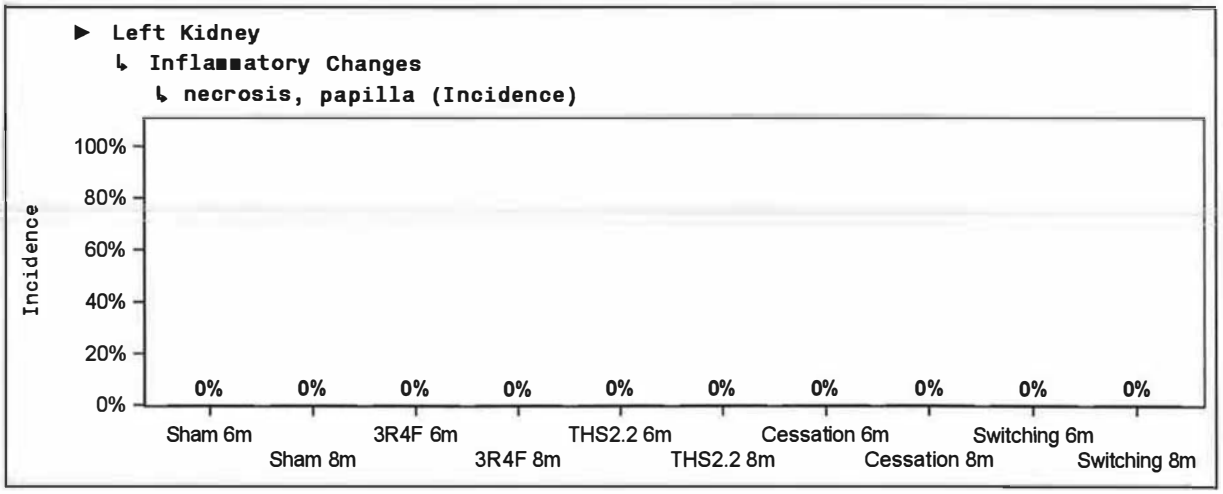


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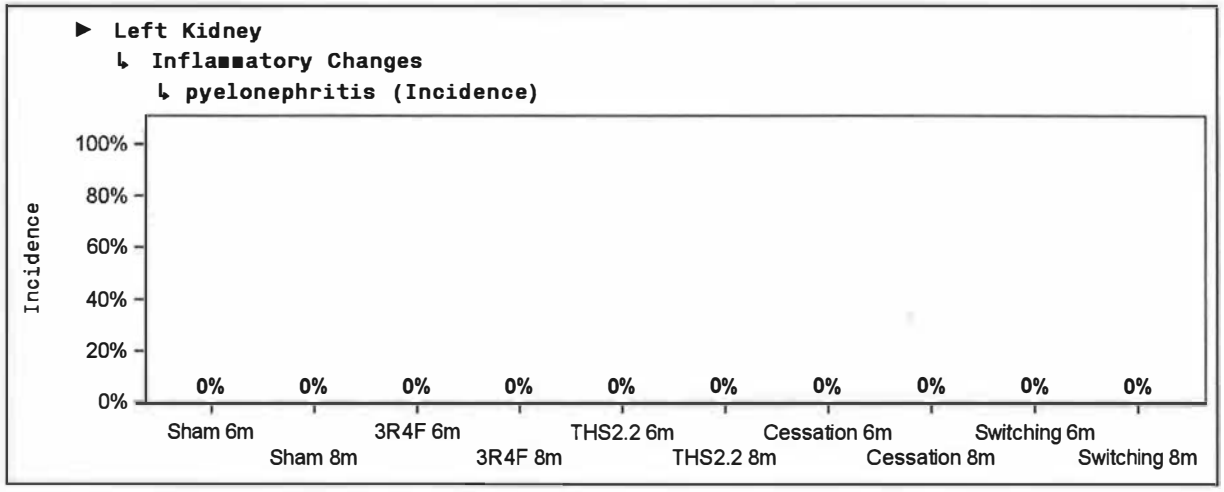


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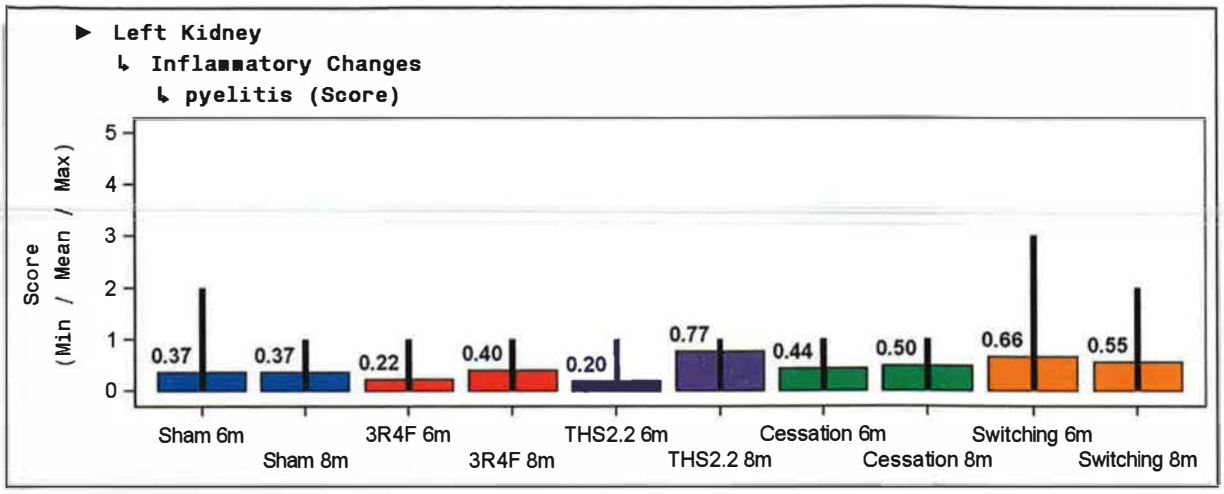


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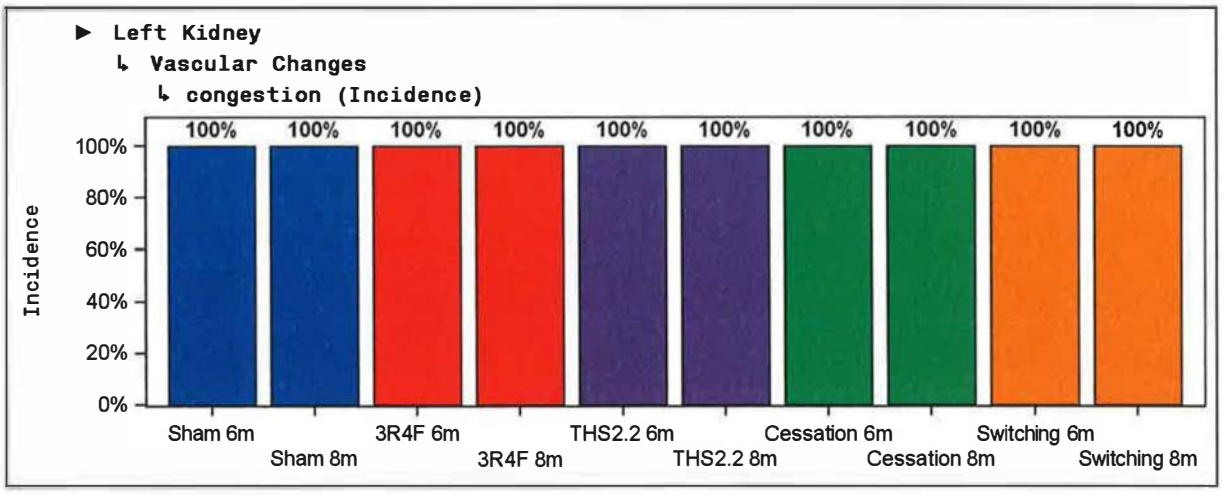


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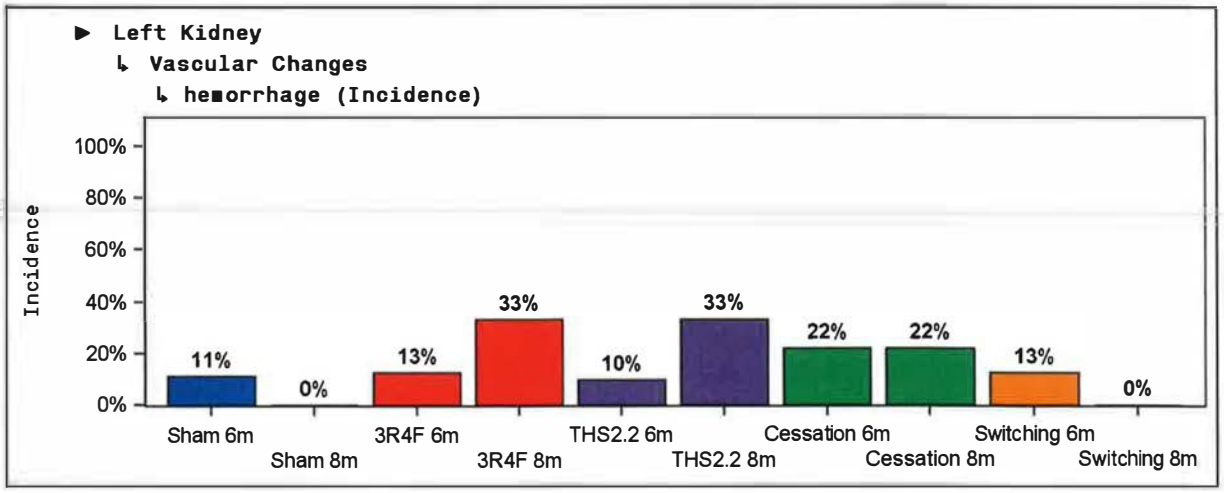


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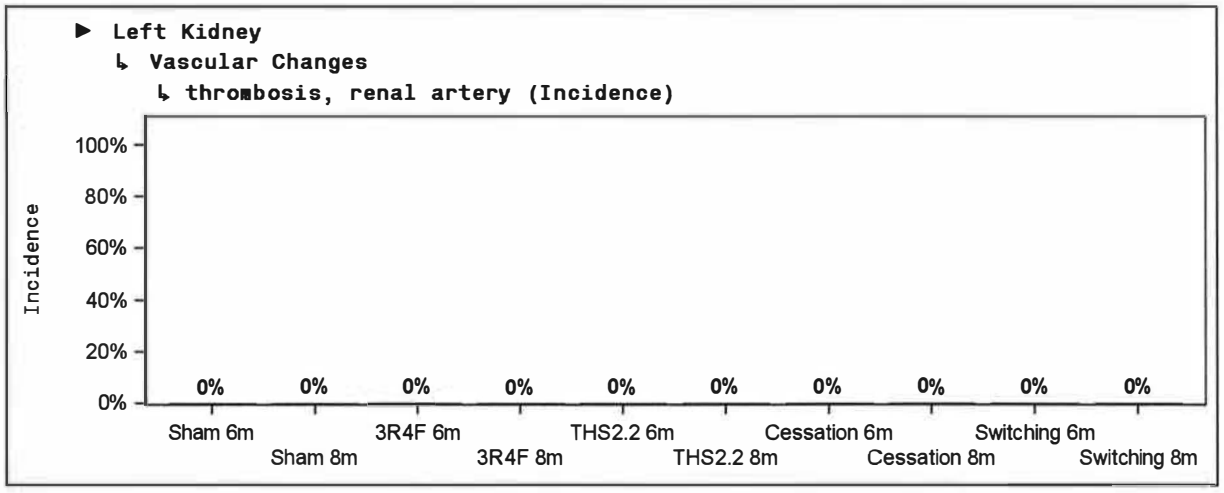


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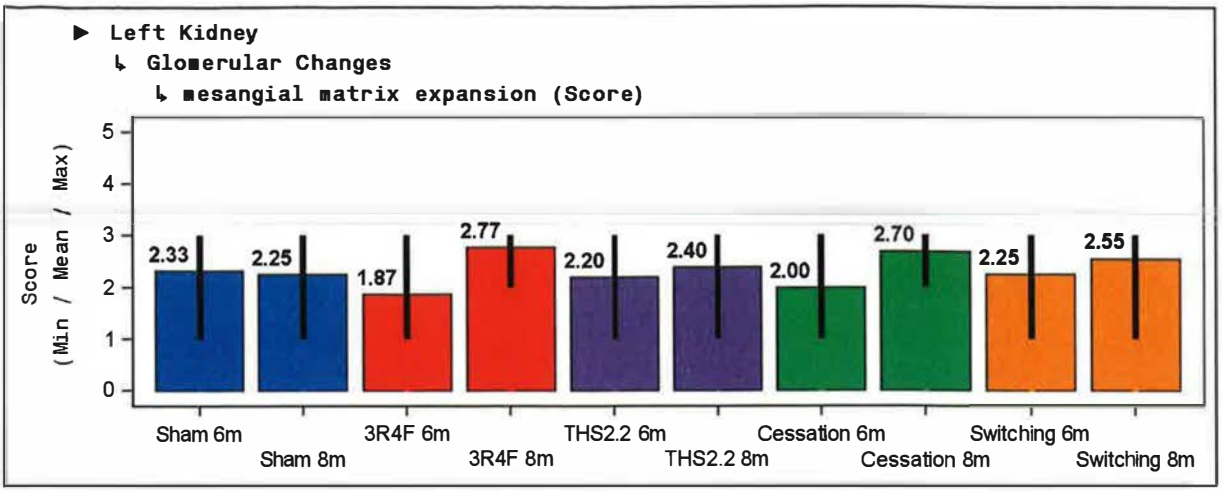


Figure 23.

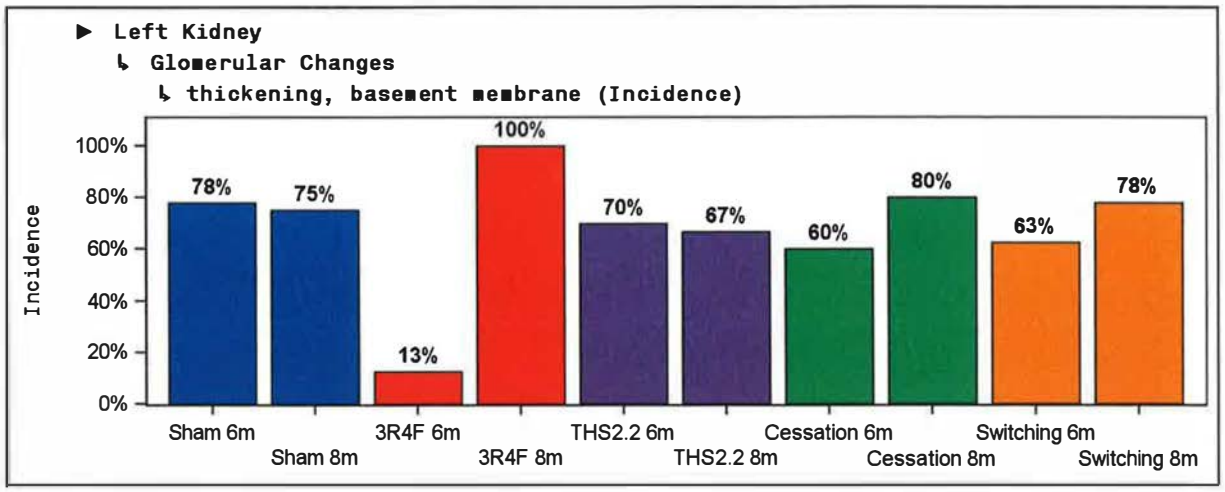


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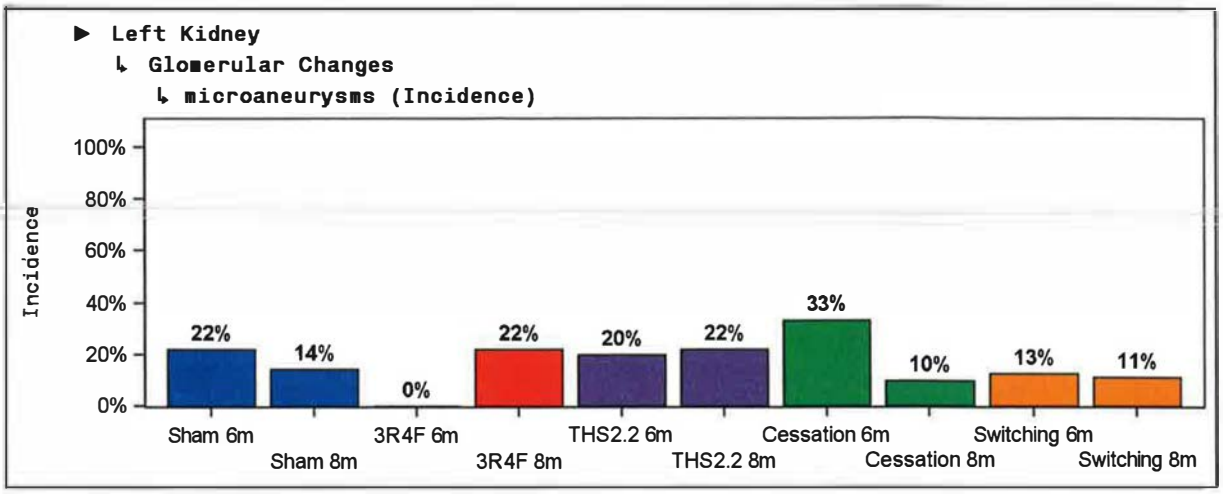


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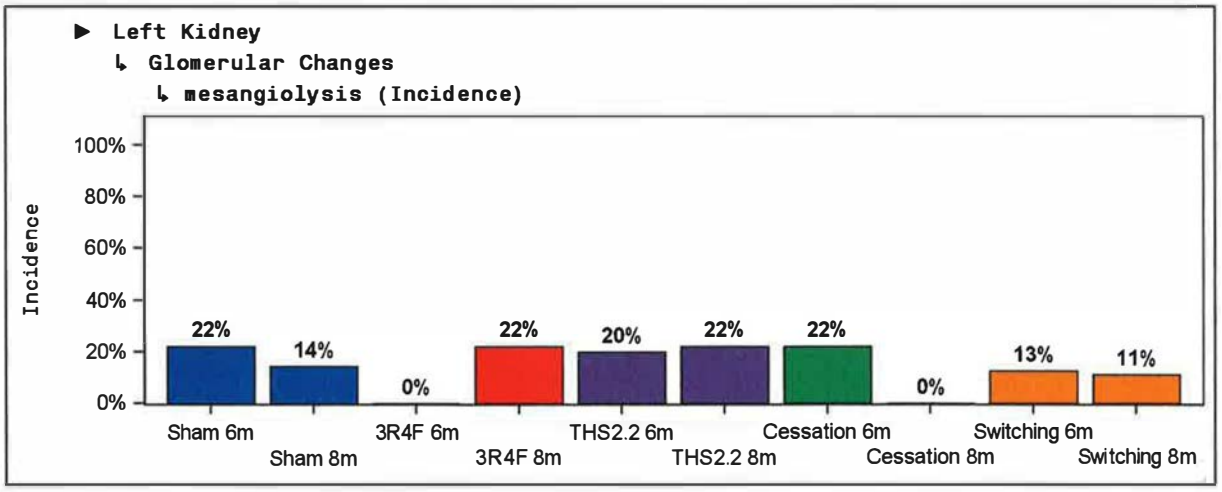


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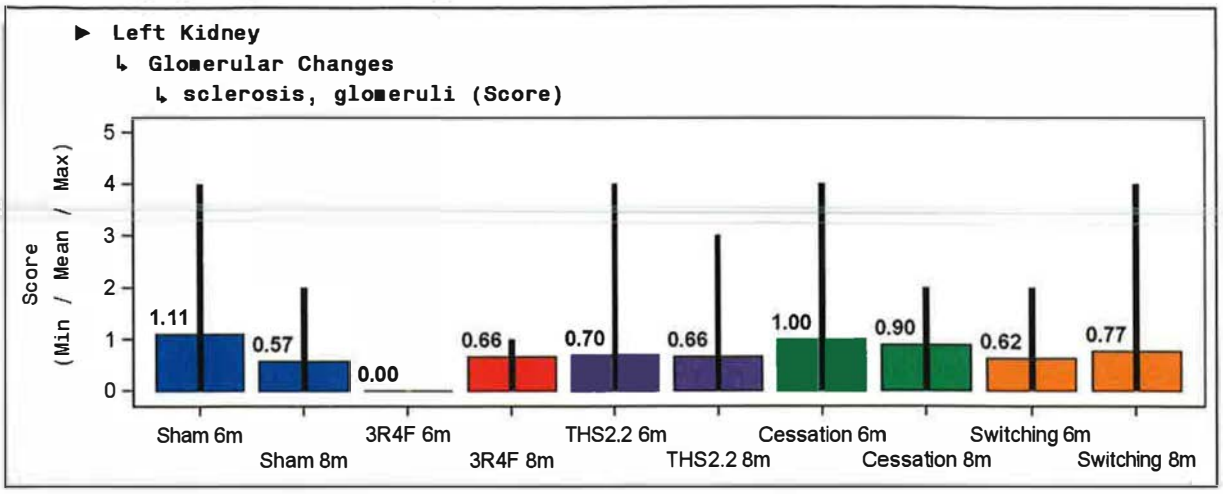


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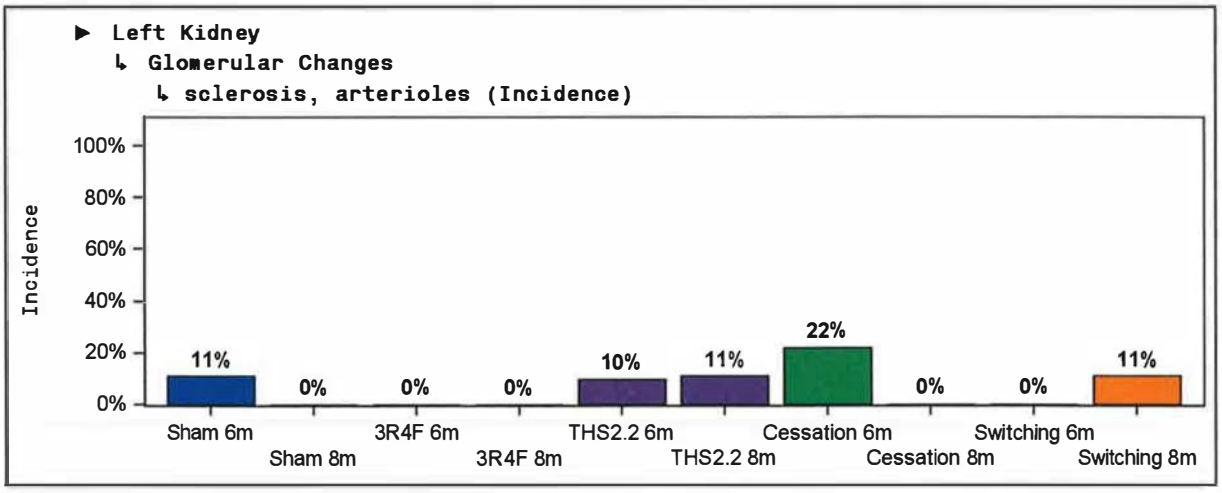


Figure 28.

9.1.1 Proportion of Incidences and Scores

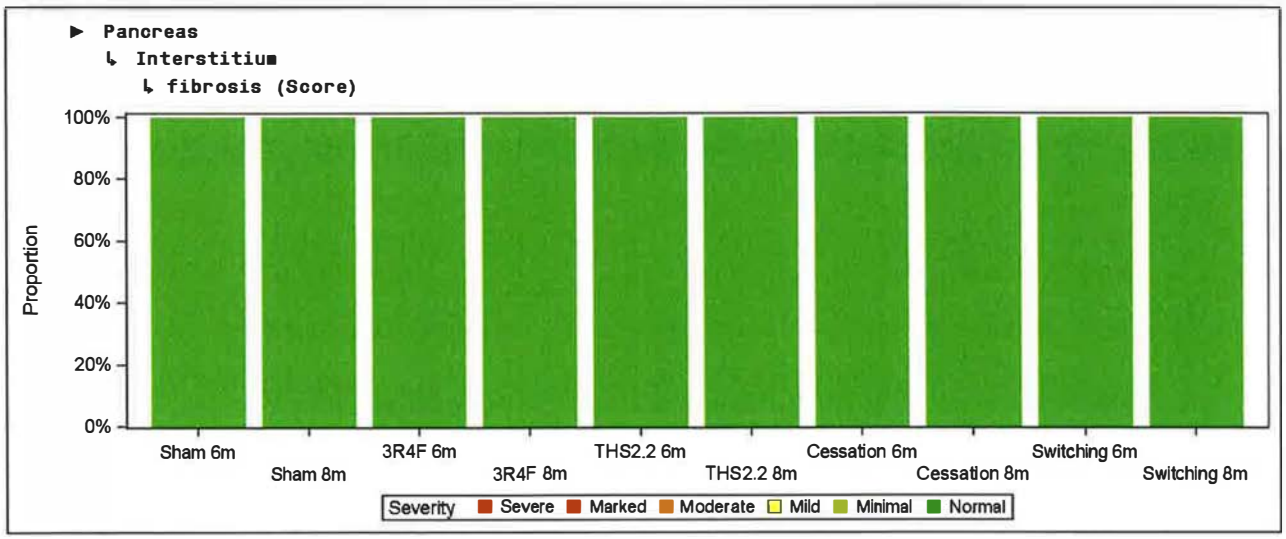


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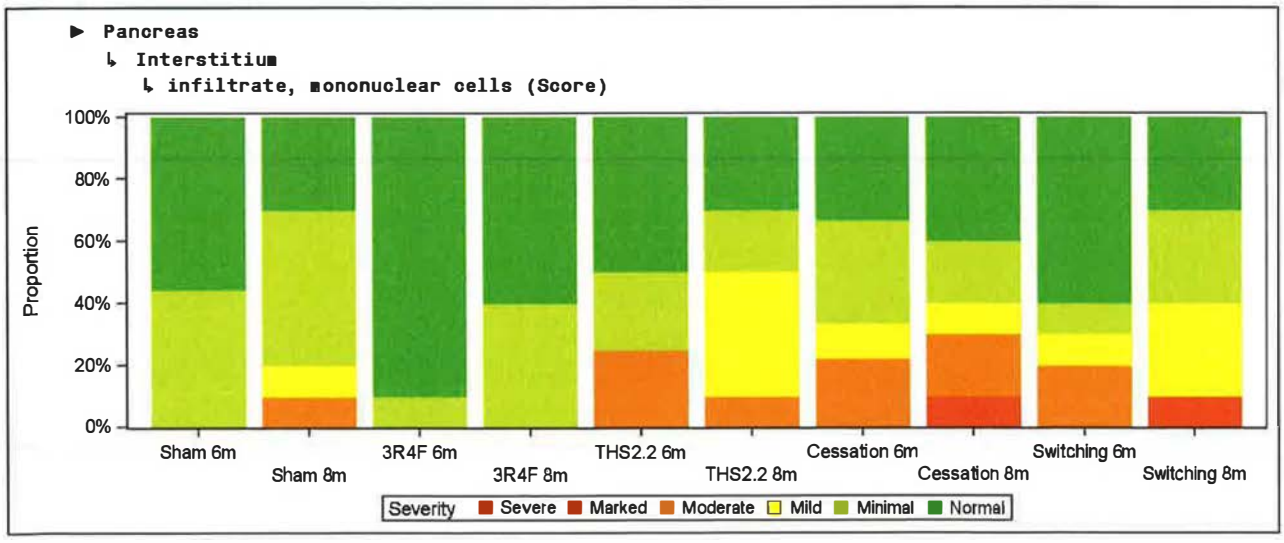


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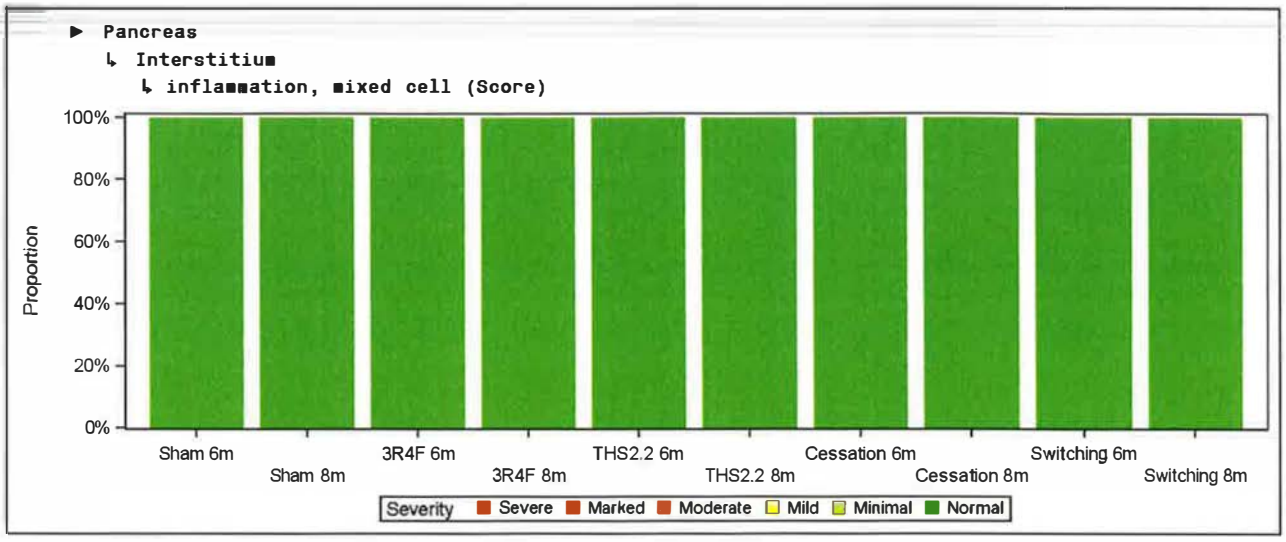


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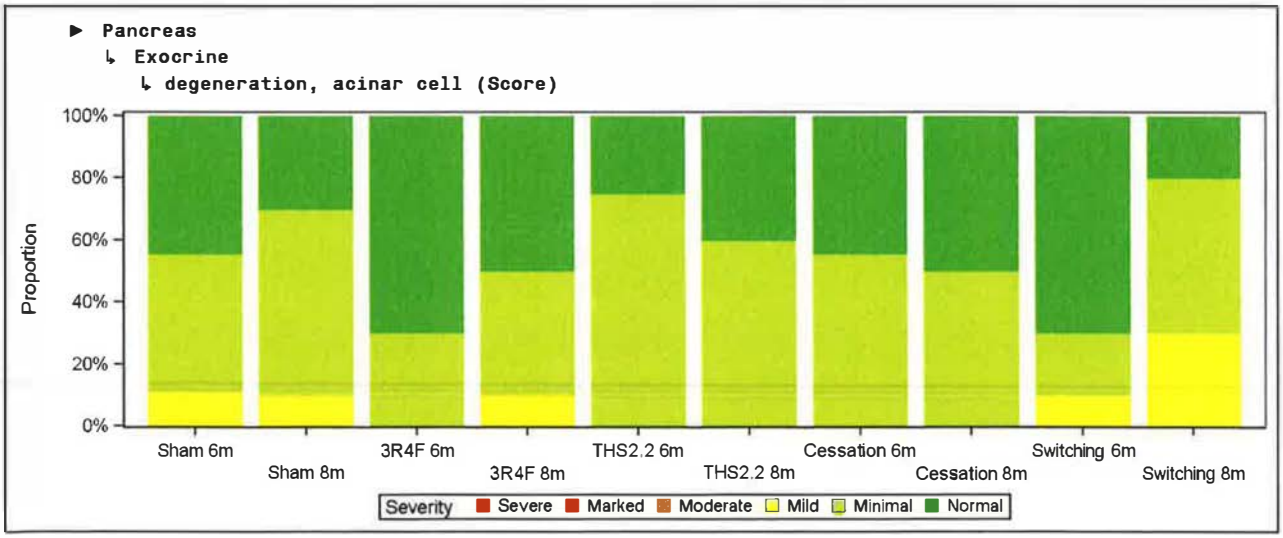


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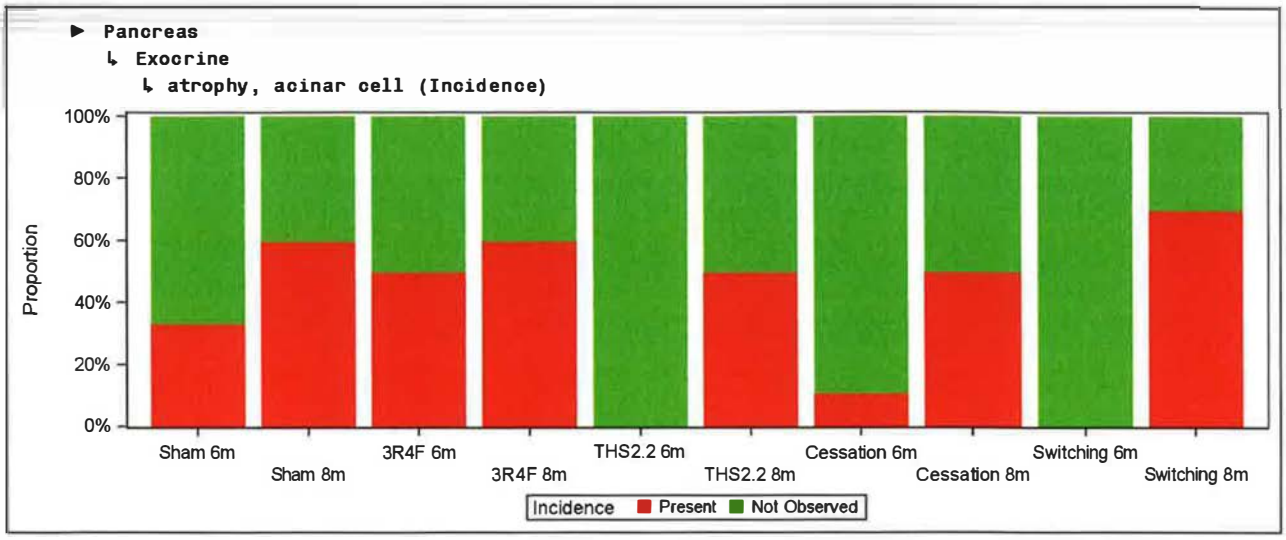


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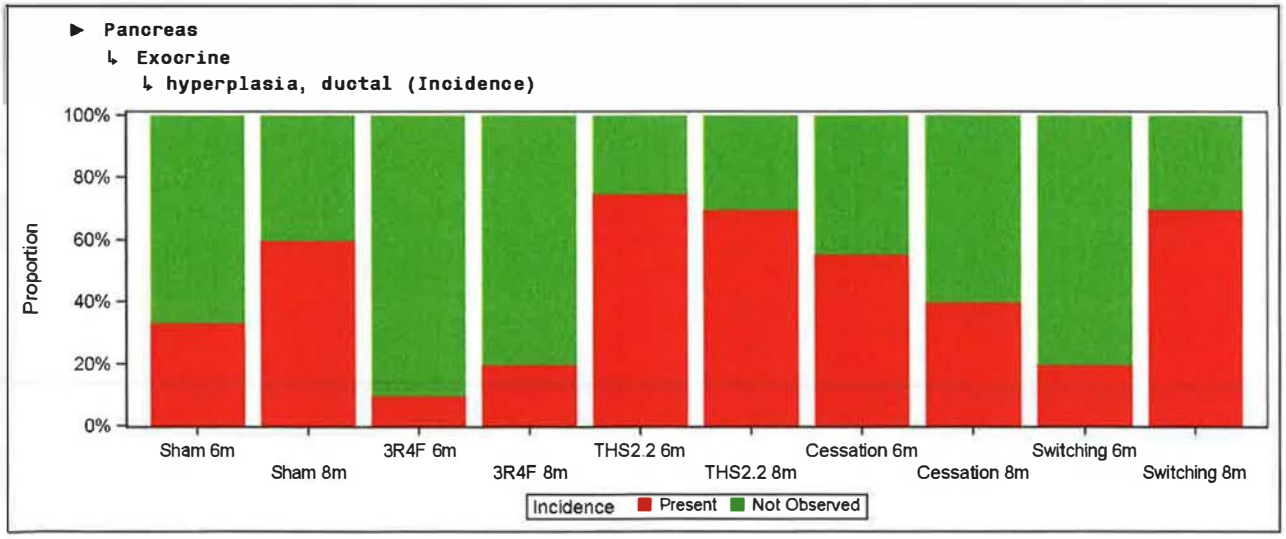


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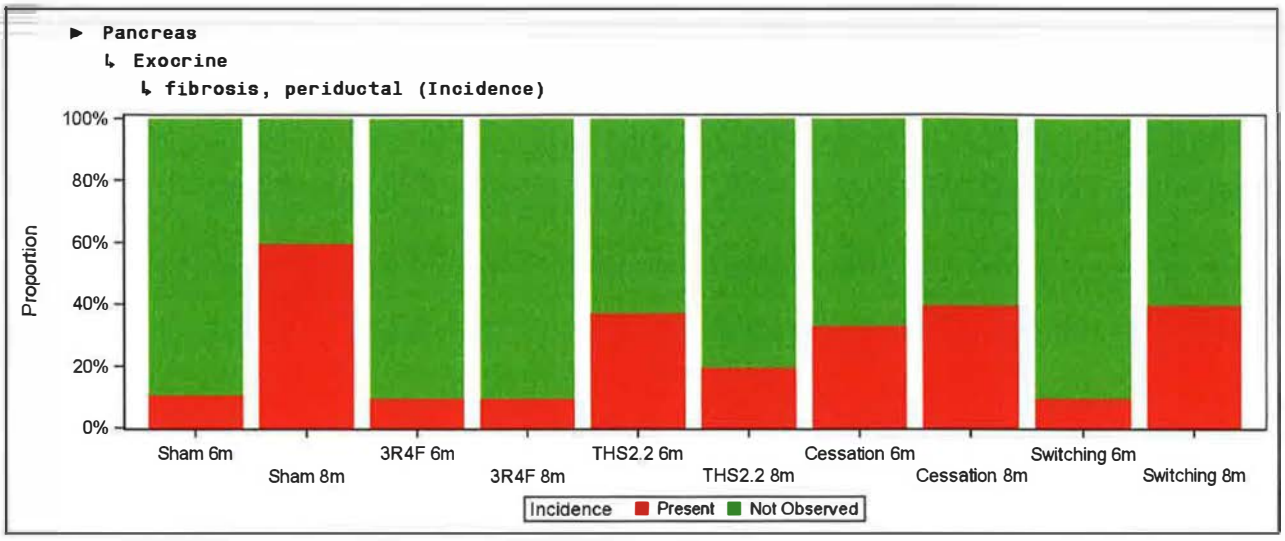


Figure 35.

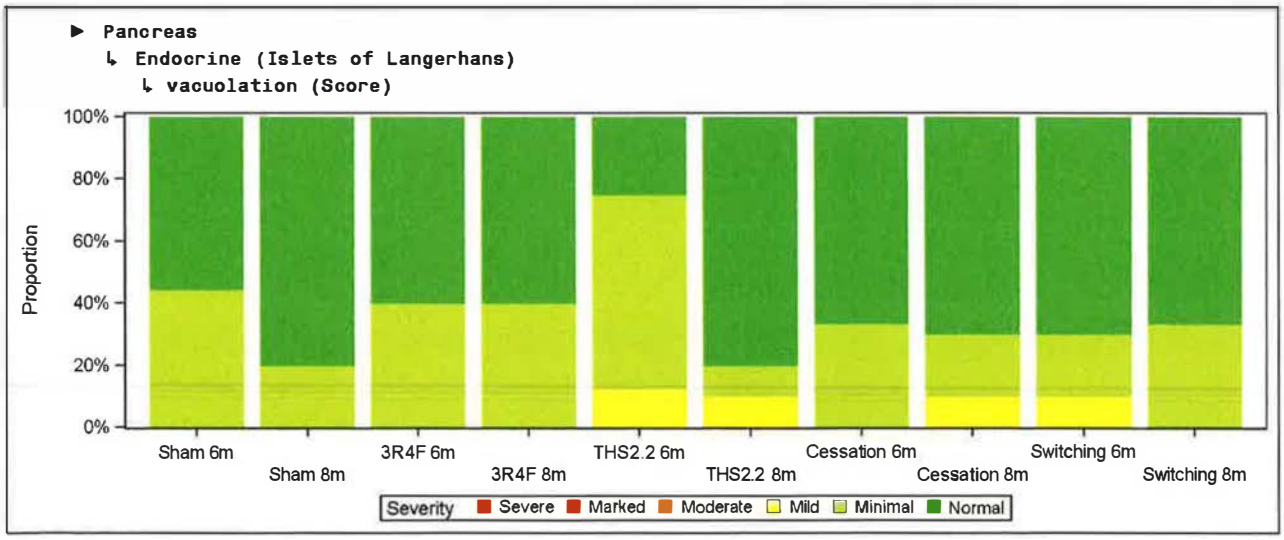


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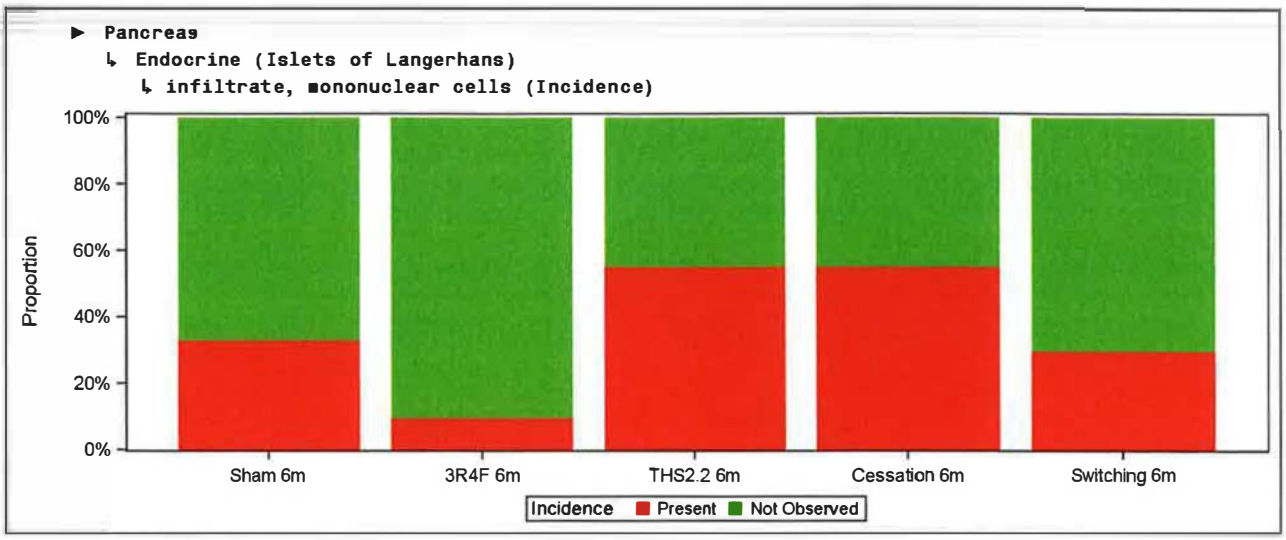


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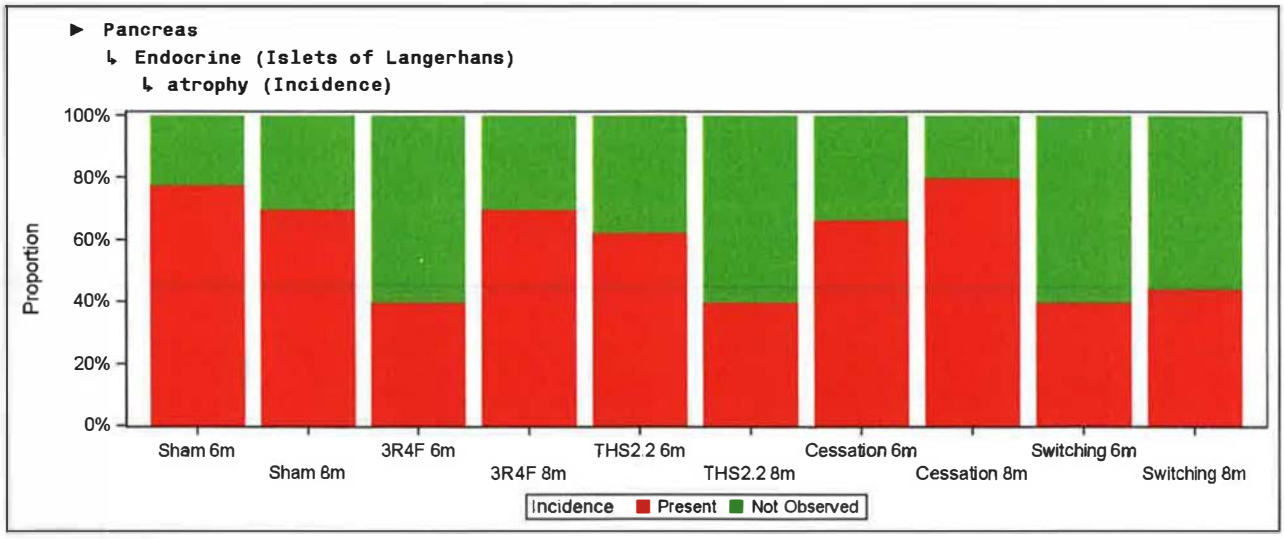


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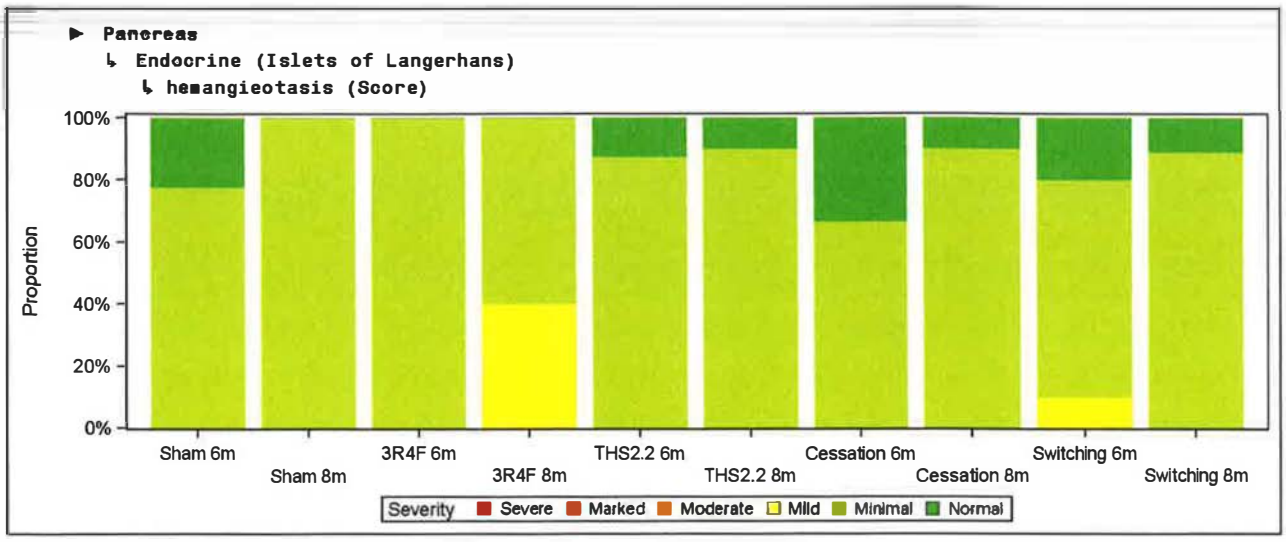


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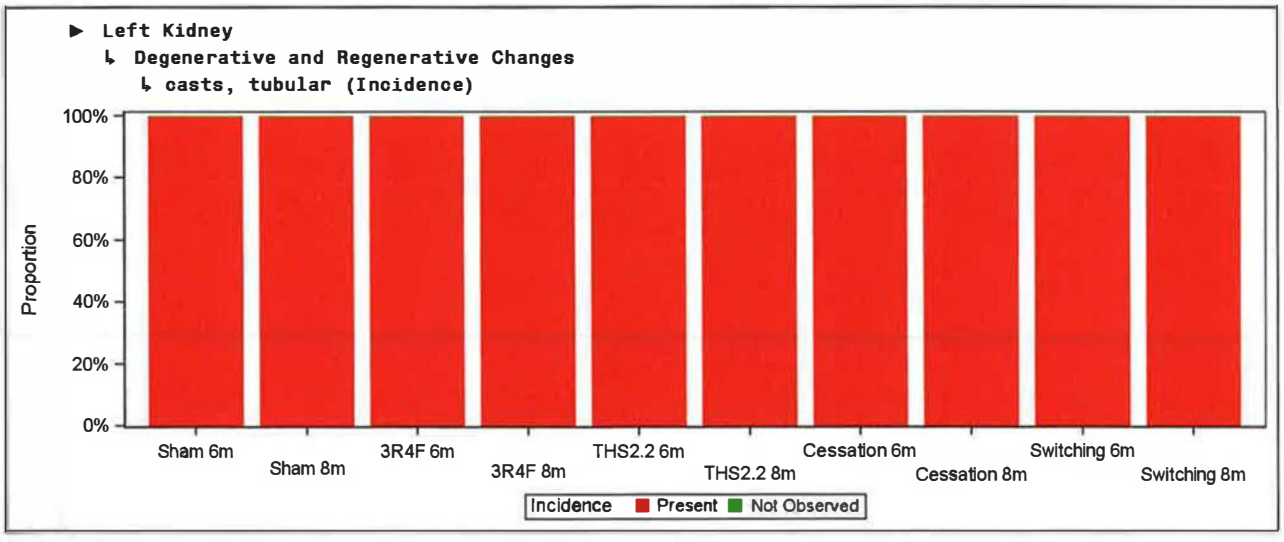


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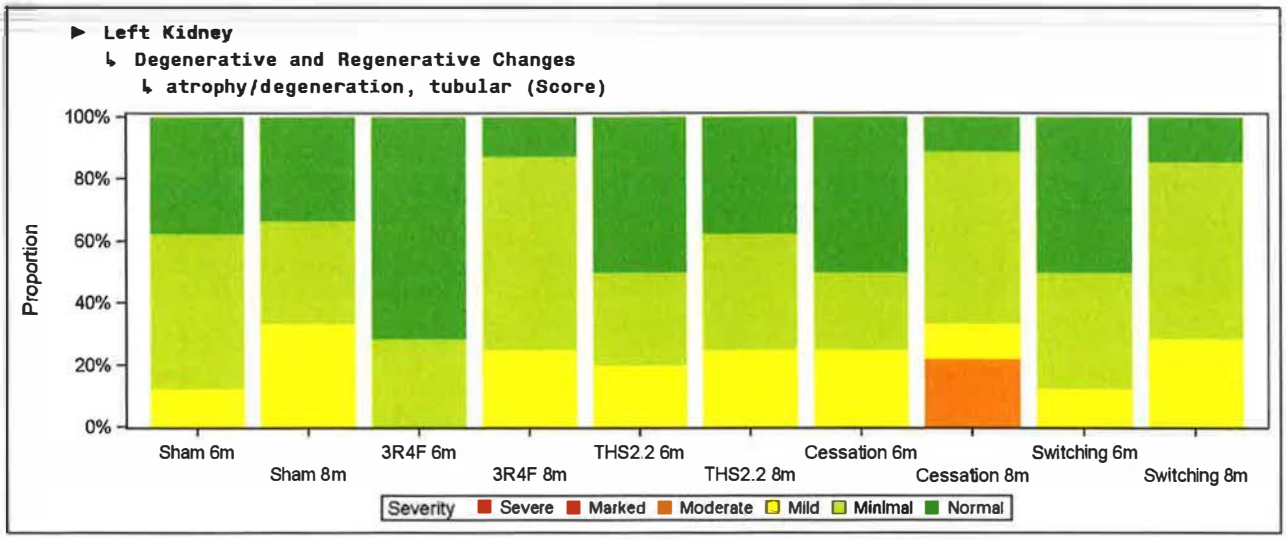


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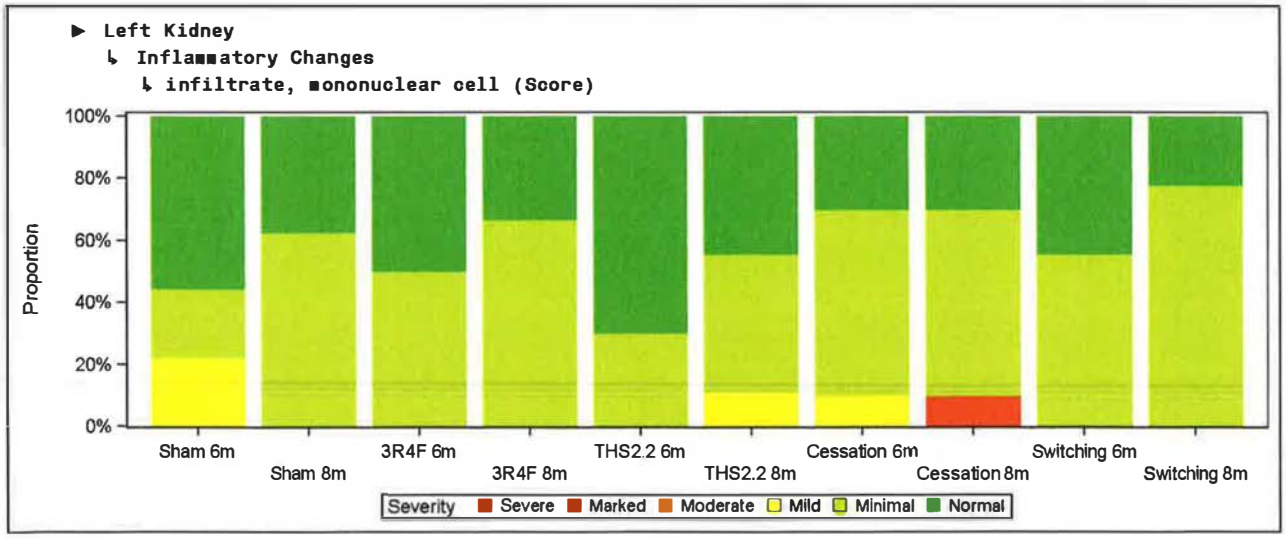


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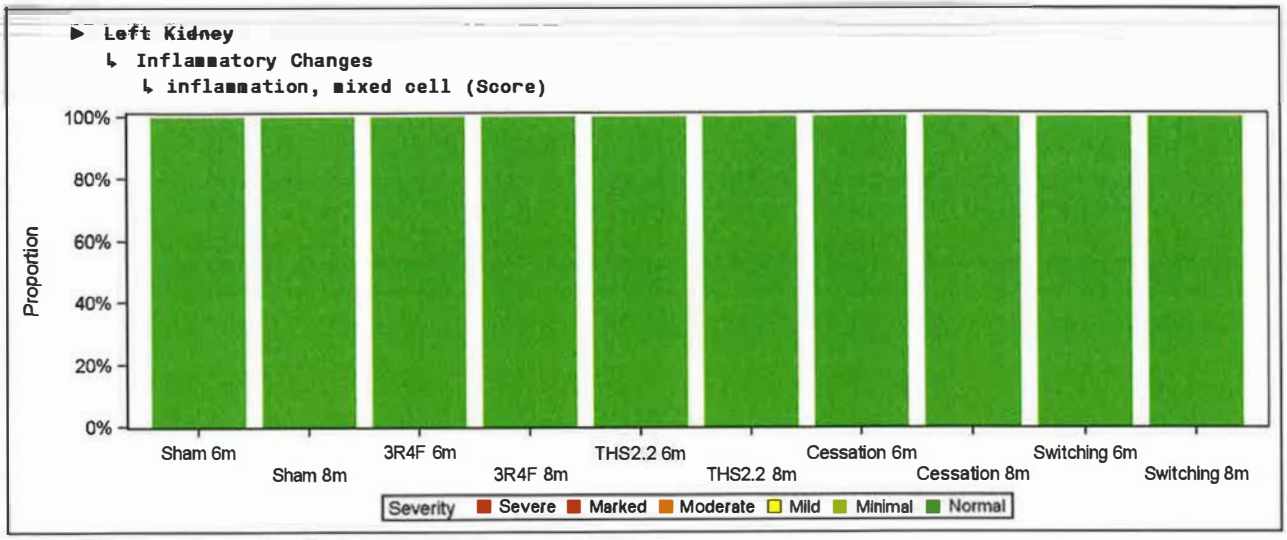


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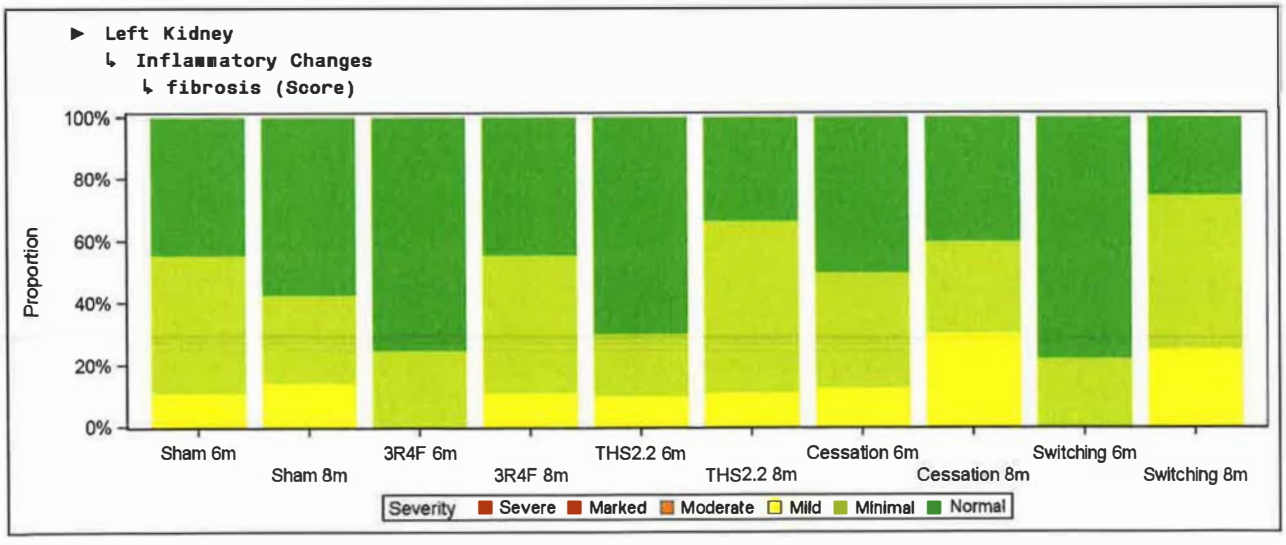


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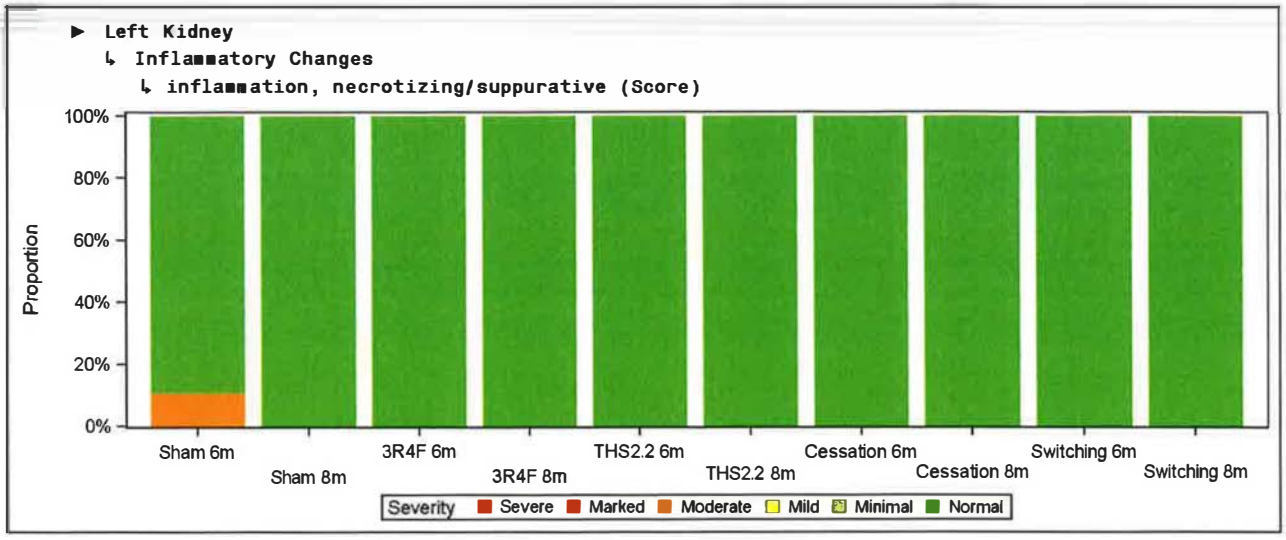


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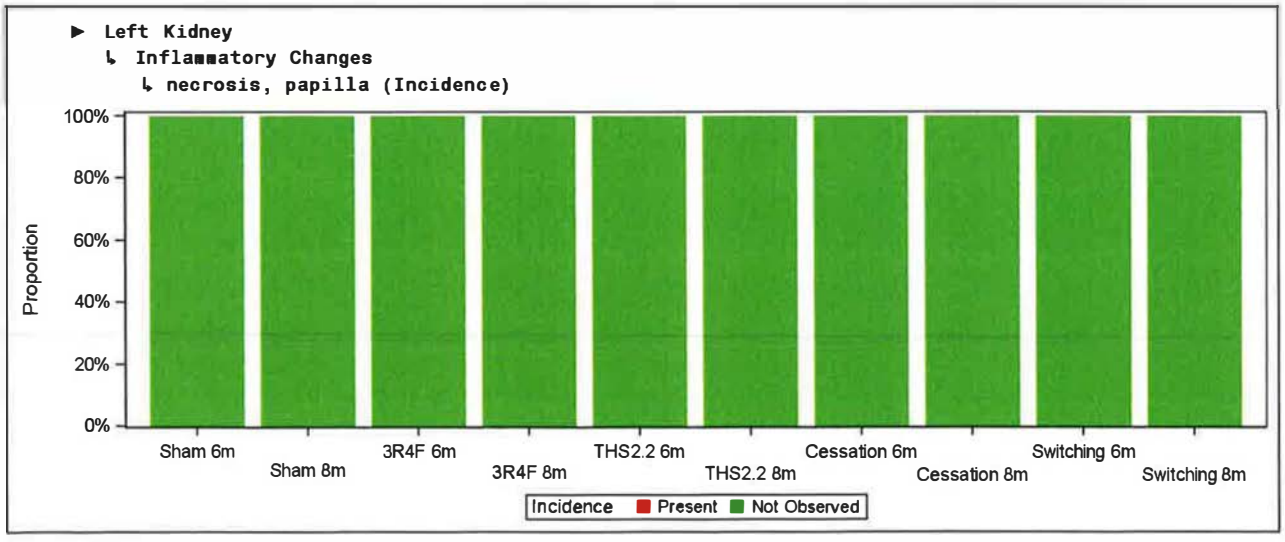


Figure 46.

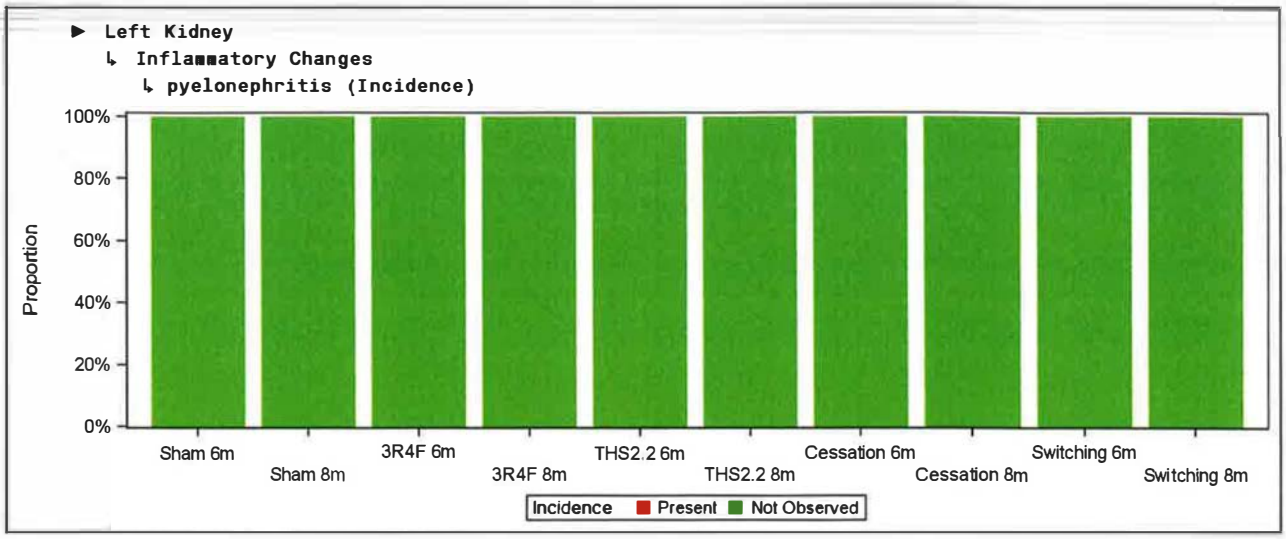


Figure 47.

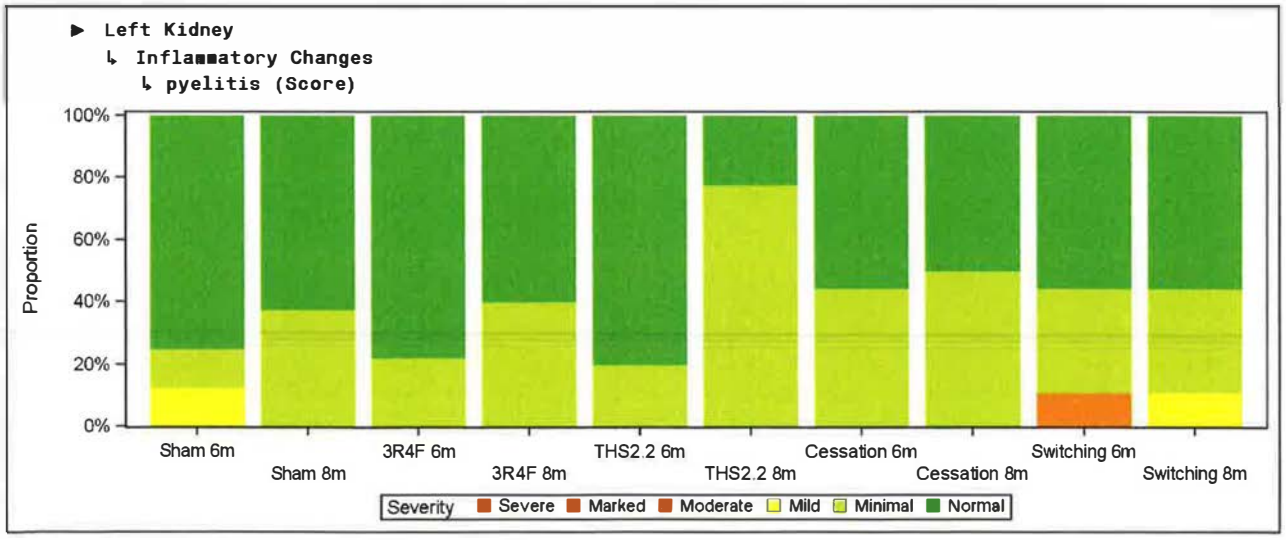


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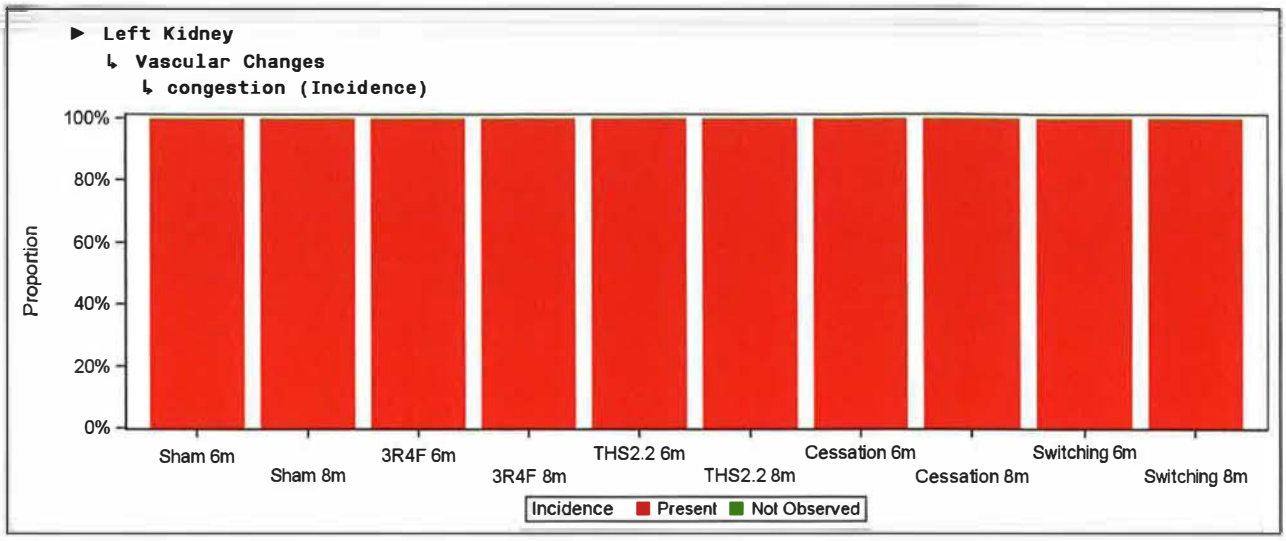


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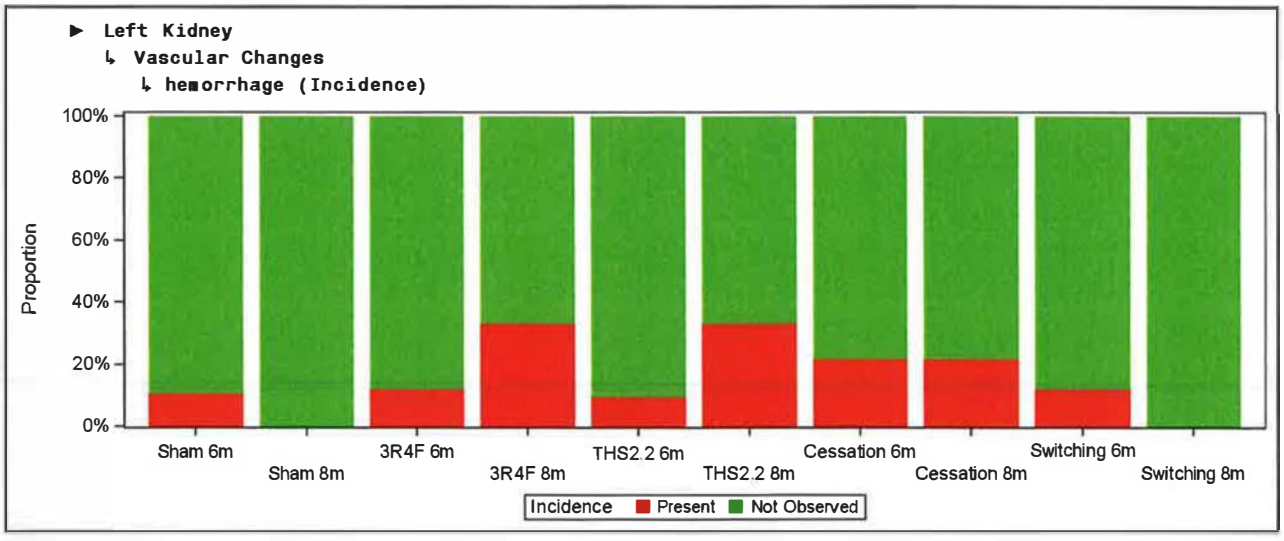


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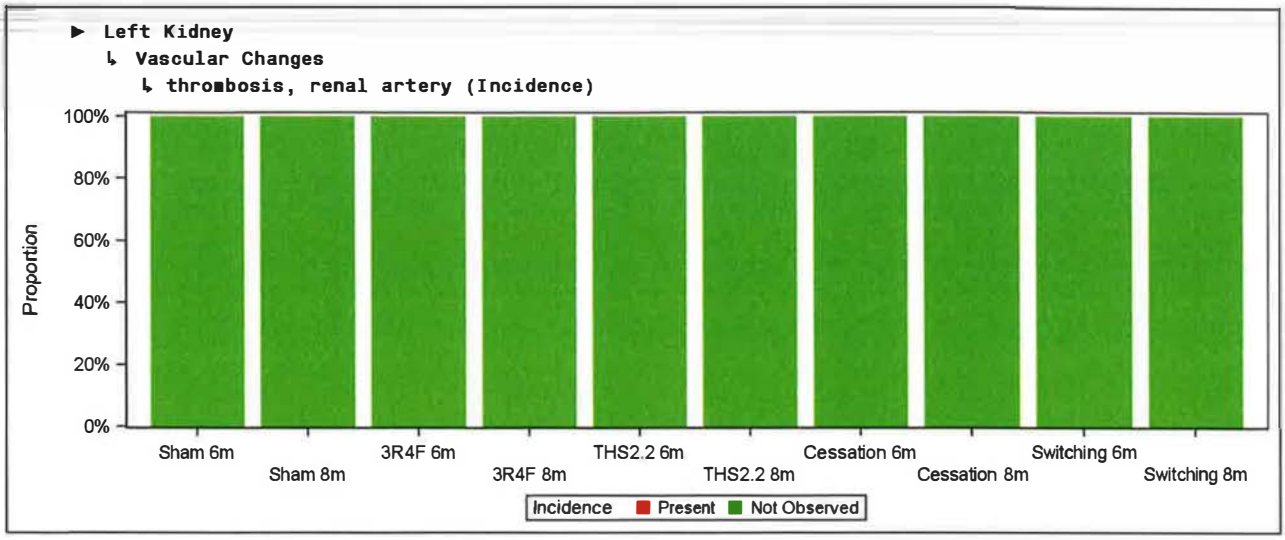


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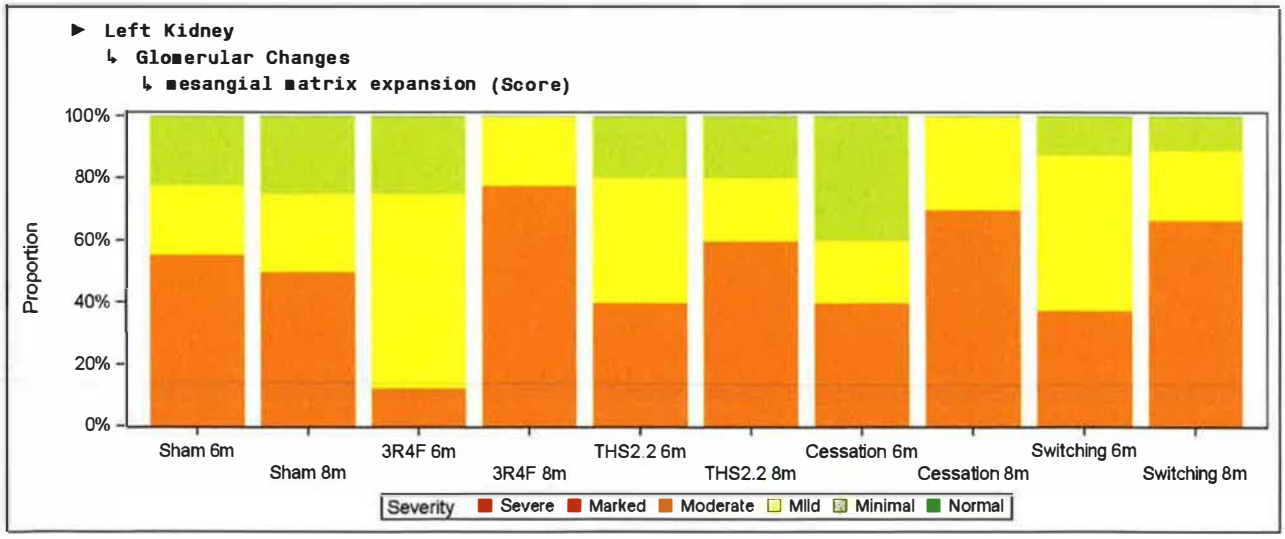


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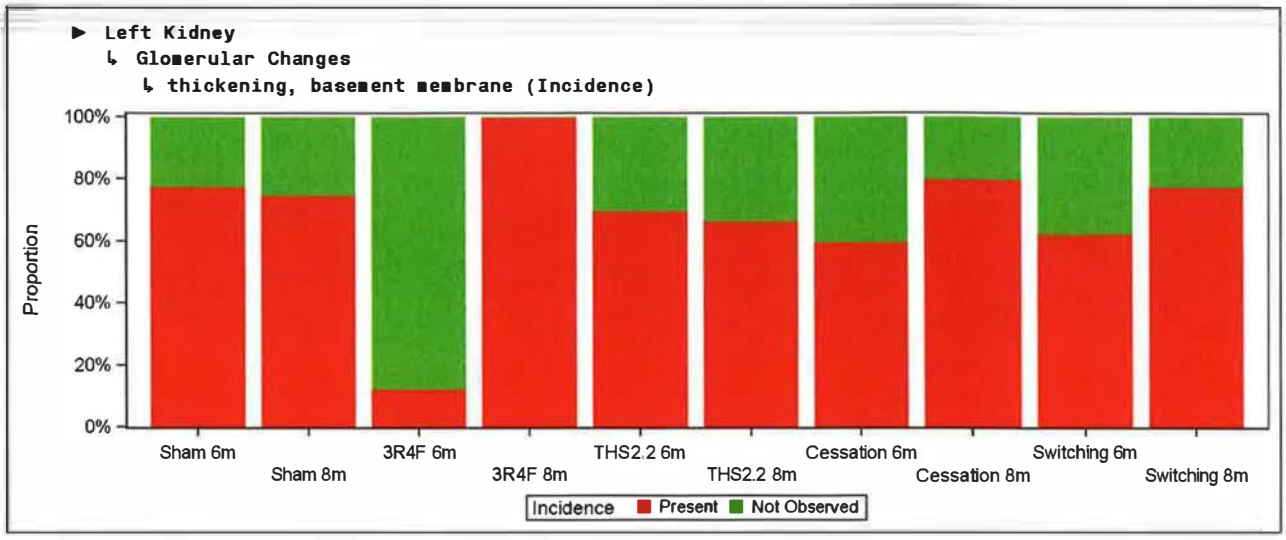


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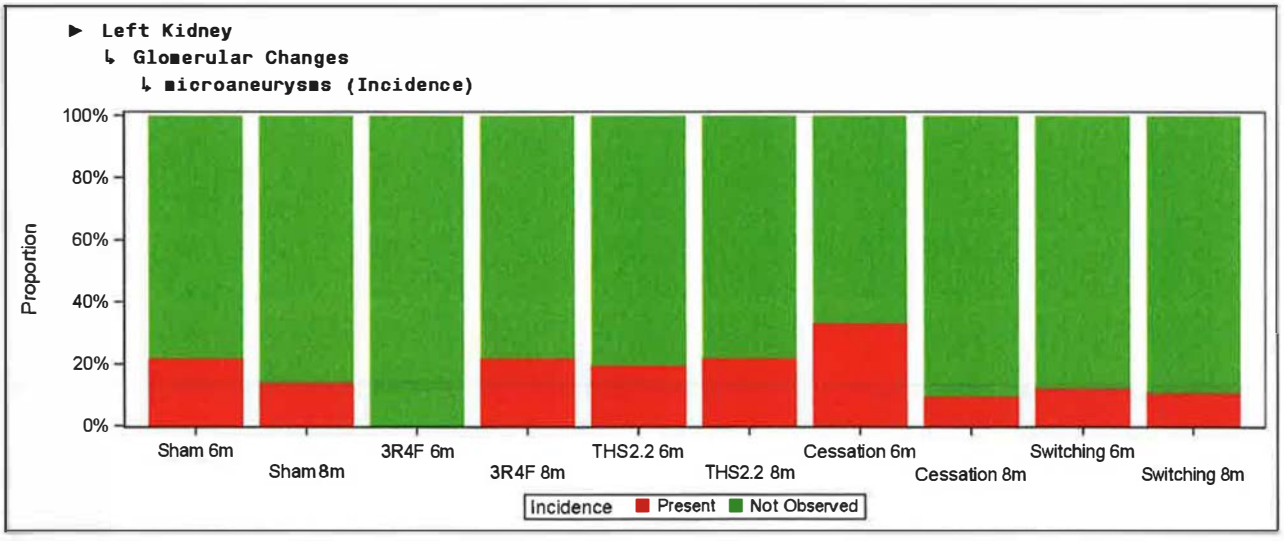


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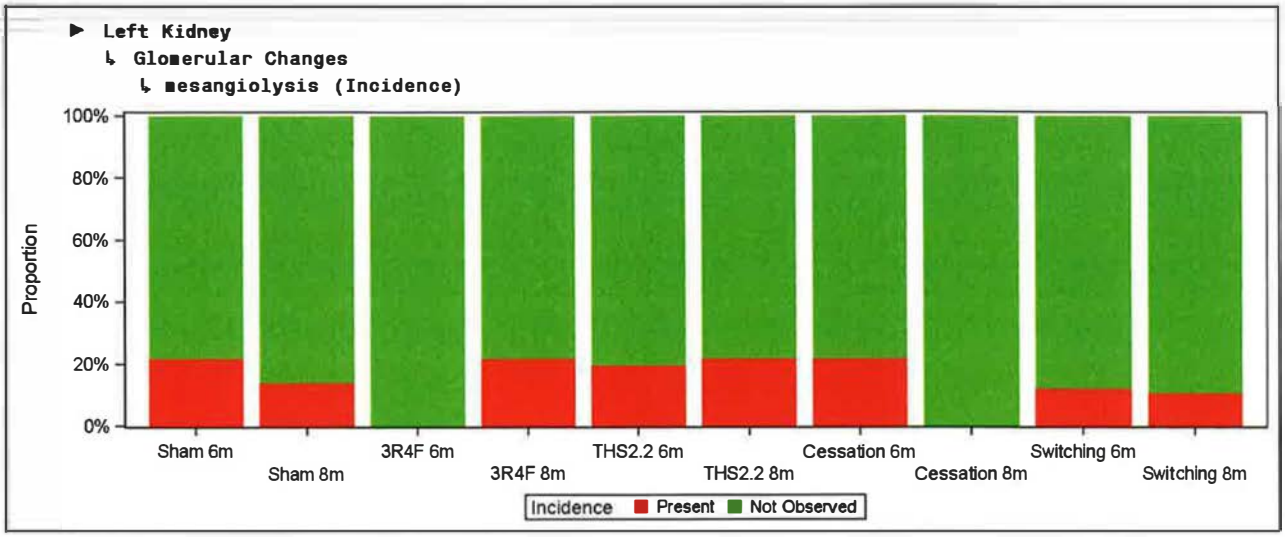


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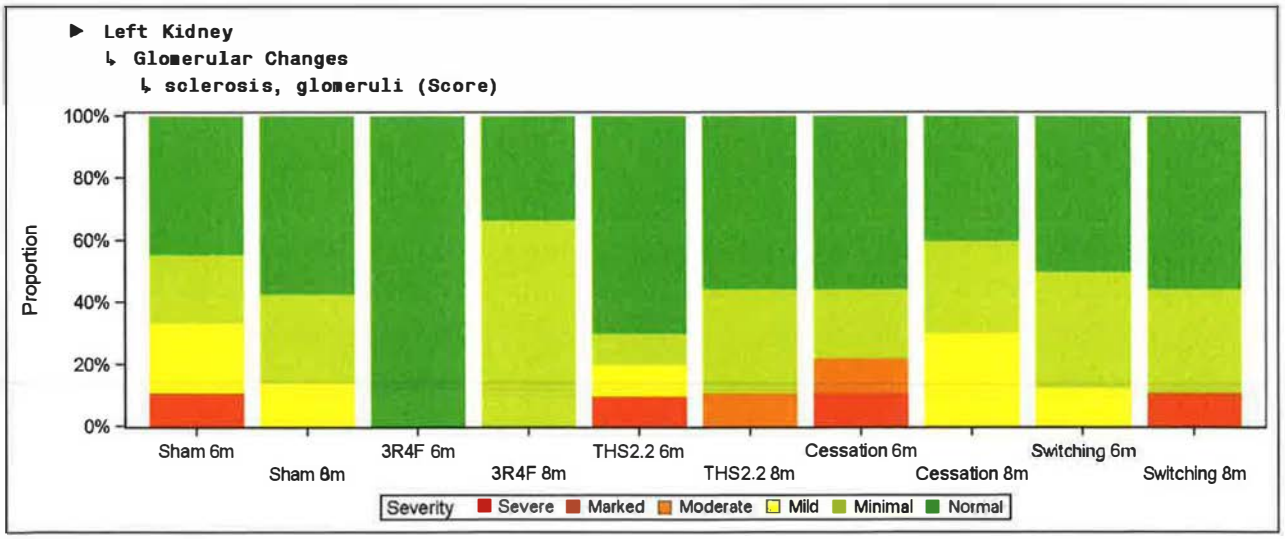


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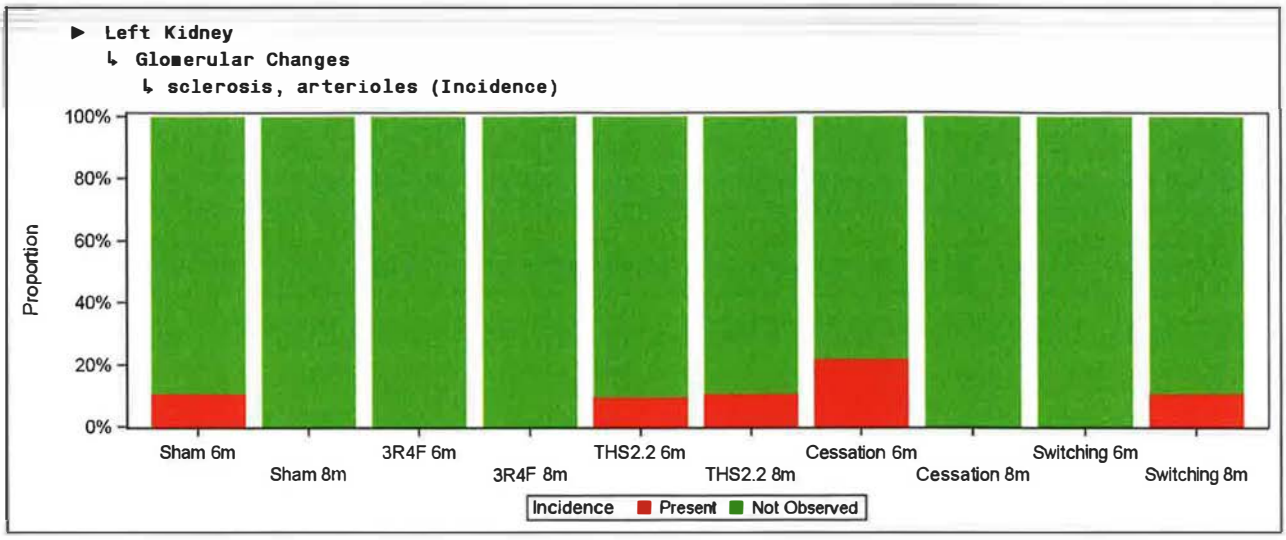

▶ Left Kidney
↳ Glomerular Changes
↳ sclerosis, arterioles (Incidence)
Proportion
100%
80%
60%
40%
20%
0%
Sham 6m
Sham 8m
3R4F 6m
3R4F 8m
THS2.2 6m
THS2.2 8m
Cessation 6m
Cessation 8m
Switching 6m
Switching 8m
Incidence
Present
Not Observed

Figure 57.

Table 14. Pancreas, descriptive statistics – group means

		6m					8m				
		Sham	3R4F	THS2.2	Cessation	Switch	Sham	3R4F	THS2.2	Cessation	Switch
Pancreas											
Interstitium											
fibrosis	Score	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
infiltrate,	Score	0.4±0.1	0.1±0.1	1.0±0.4	1.2±0.4	0.9±0.4	1.0±0.3	0.4±0.1	1.3±0.3	1.4±0.4	1.3±0.4
inflammatio	Score	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Exocrine											
degeneratio	Score	0.7±0.2	0.3±0.1	0.8±0.1	0.6±0.1	0.4±0.2	0.8±0.2	0.6±0.2	0.6±0.1	0.5±0.1	1.1±0.2
atrophy,	Incidenc	0.3	0.5	0.0	0.1	0.0	0.6	0.6	0.5	0.5	0.7
hyperplasia	Incidenc	0.3	0.1	0.8	0.6	0.2	0.6	0.2	0.7	0.4	0.7
fibrosis,	Incidenc	0.1	0.1	0.4	0.3	0.1	0.6	0.1	0.2	0.4	0.4
Endocrine											
vacuolation	Score	0.4±0.1	0.4±0.1	0.9±0.2	0.3±0.1	0.4±0.2	0.2±0.1	0.4±0.1	0.3±0.2	0.4±0.2	0.3±0.1
infiltrate,	Incidenc	0.3	0.1	0.6	0.6	0.3					
atrophy	Incidenc	0.8	0.4	0.6	0.7	0.4	0.7	0.7	0.4	0.8	0.4
hemangiecta	Score	0.8±0.1	1.0±0.0	0.9±0.1	0.7±0.1	0.9±0.1	1.0±0.0	1.4±0.1	0.9±0.1	0.9±0.1	0.9±0.1

Table 15. Kidney, descriptive statistics – group means

		6m					8m				
		Sham	3R4F	THS2.2	Cessation	Switch	Sham	3R4F	THS2.2	Cessation	Switch
Left Kidney											
Degenerative and											
casts, tubular	Inciden	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
atrophy/degenera	Score	0.8±0.	0.3±0.	0.7±0.	0.8±0.3	0.6±0.	1.0±0.	1.1±0.	0.9±0.	1.4±0.3	1.1±0.
Inflammatory											
Interstitium											
infiltrate,	Score	0.7±0.	0.5±0.	0.3±0.	0.8±0.2	0.6±0.	0.6±0.	0.7±0.	0.7±0.	1.0±0.3	0.8±0.
inflammation,	Score	0.0±0.	0.0±0.	0.0±0.	0.0±0.0	0.0±0.	0.0±0.	0.0±0.	0.0±0.	0.0±0.0	0.0±0.
fibrosis	Score	0.7±0.	0.3±0.	0.4±0.	0.6±0.2	0.2±0.	0.6±0.	0.7±0.	0.8±0.	0.9±0.2	1.0±0.
inflammation,	Score	0.3±0.	0.0±0.	0.0±0.	0.0±0.0	0.0±0.	0.0±0.	0.0±0.	0.0±0.	0.0±0.0	0.0±0.
Medulla											
necrosis,	Inciden	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
pyelonephriti	Inciden	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
pyelitis	Score	0.4±0.	0.2±0.	0.2±0.	0.4±0.1	0.7±0.	0.4±0.	0.4±0.	0.8±0.	0.5±0.1	0.6±0.
Vascular Changes											
congestion	Inciden	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
hemorrhage	Inciden	0.1	0.1	0.1	0.2	0.1	0.0	0.3	0.3	0.2	0.0
thrombosis,	Inciden	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Glomerular Changes											
mesangial matrix	Score	2.3±0.	1.9±0.	2.2±0.	2.0±0.3	2.3±0.	2.3±0.	2.8±0.	2.4±0.	2.7±0.1	2.6±0.
thickening,	Inciden	0.8	0.1	0.7	0.6	0.6	0.8	1.0	0.7	0.8	0.8
microaneurysms	Inciden	0.2	0.0	0.2	0.3	0.1	0.1	0.2	0.2	0.1	0.1
mesangiolysis	Inciden	0.2	0.0	0.2	0.2	0.1	0.1	0.2	0.2	0.0	0.1
sclerosis,	Score	1.1±0.	0.0±0.	0.7±0.	1.0±0.5	0.6±0.	0.6±0.	0.7±0.	0.7±0.	0.9±0.2	0.8±0.
sclerosis,	Inciden	0.1	0.0	0.1	0.2	0.0	0.0	0.0	0.1	0.0	0.1

Table 16. Inferential Statistics- Pairwise Comparisons

		Pairwise Comparisons																							
		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
Finding	Type																									
Left Kidney																										
Degenerative and Regenerative Changes																										
atrophy/degeneration, tubular	Score																						1			
Inflammatory Changes																										
Interstitium																										
fibrosis	Score																									1
Medulla																										
pyelitis	Score																						1			
Vascular Changes																										
Glomerular Changes																										
mesangial matrix expansion	Score																						2			
thickening, basement membrane	Incidence	1								1													3			
sclerosis, glomeruli	Score	1										1		1									2			
Pancreas																										
Interstitium																										
infiltrate, mononuclear cells	Score										1	1														
Exocrine																										
degeneration, acinar cell	Score																									1
atrophy, acinar cell	Incidence									1				1										1		2
hyperplasia, ductal	Incidence									1																
Endocrine (Islets of Langerhans)																										
vacuolation	Score																							1		
hemangiectasis	Score		1								1		1		1								1			

- Comparisons :

(A) = Sham vs. 3R4F / 6m , (B) = Sham vs. 3R4F / 8m , (C) = Sham vs. THS2.2 / 6m , (D) = Sham vs. THS2.2 / 8m , (E) = Sham vs. Cessation / 6m , (F) = Sham vs. Cessation / 8m , (G) = Sham vs. Switch / 6m , (H) = Sham vs. Switch / 8m , (I) = 3R4F vs. THS2.2 / 6m , (J) = 3R4F vs. THS2.2 / 8m , (K) = 3R4F vs. Cessation / 6m , (L) = 3R4F vs. Cessation / 8m , (M) = 3R4F vs. Switch / 6m , (N) = 3R4F vs. Switch / 8m , (O) = THS2.2 vs. Cessation / 6m , (P) = THS2.2 vs. Cessation / 8m , (Q) = THS2.2 vs. Switch / 6m , (R) = THS2.2 vs. Switch / 8m , (S) = Cessation vs. Switch / 6m , (T) = Cessation vs. Switch / 8m , (U) = Sham / 6m vs. 8m , (V) = 3R4F / 6m vs. 8m , (W) = THS2.2 / 6m vs. 8m , (X) = Cessation / 6m vs. 8m , (Y) = Switch / 6m vs. 8m

- Scores are tested using Cochran-Mantel-Haenszel test on the row mean score difference
- Incidences are tested using the Fisher exact test
- P-values less or equal than 0.05, 0.01 and 0.001 are respectively reported as '1', '2' and '3'

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