

1 **Efficacy and safety of a monodisperse solid-in-oil-in-water emulsion in**
2 **transcatheter arterial chemoembolization in a rabbit VX2 tumor model**

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4 **Short title:** Monodisperse emulsion in transarterial therapy

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6 Daisuke Yasui^{1*}, Aya Yamane^{2¶}, Hiroshi Itoh^{3¶}, Masayuki Kobayashi^{3¶}, Shin-ichiro Kumita^{1&}

7

8 ¹ Department of Radiology, Nippon Medical School, Tokyo, Japan

9 ² Department of Radiology, Nippon Medical School Musashi Kosugi Hospital, Kawasaki,
10 Kanagawa, Japan

11 ³ Advanced Animal Medical Center, Suntou-gun, Shizuoka, Japan

12

13 * Corresponding author

14 E-mail: ledhotcp@nms.ac.jp (DY)

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16 ¶These authors contributed equally to this work.

17 &These authors also contributed equally to this work.

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19 **Abstract**

20 Transcatheter arterial chemoembolization (TACE) is a standard treatment for
21 unresectable hepatocellular carcinoma; however, it does not always result in tumor control.
22 Nevertheless, treatment outcome can be improved with monodisperse emulsions of anticancer
23 agents. In this study, the efficacy and safety of a monodisperse miriplatin-Lipiodol emulsion
24 were evaluated in Japanese white rabbits. VX2 tumor was implanted into the left liver lobe of
25 each rabbit. The animals were divided into control and experimental groups (of five animals
26 each) and respectively administered a conventional miriplatin suspension or the emulsion via
27 the left hepatic artery. Computed tomography (CT) was performed before, immediately after,
28 and two days following TACE. All rabbits were sacrificed two days after the procedure. Each
29 tumor was removed and cut in half for assessment of iodine concentration in one half by mass
30 spectroscopy and evaluation of Lipiodol accumulation and adverse events in the other half.
31 Mean Hounsfield unit (HU) values were measured using plain CT images taken before and
32 after TACE. Iodine concentration was higher in the experimental group [1100 (750–1500)
33 ppm] than in the control group [840 (660–1800) ppm]. Additionally, the HU value for the
34 experimental group was higher than that for the control group immediately after [199.6 (134.0–
35 301.7) vs. 165.3 (131.4–280.5)] and two days after [114.2 (56.1–229.8) vs. 58.3 (42.9–132.5)]
36 TACE. Cholecystitis was observed in one rabbit in the control group. Ischemic bile duct injury
37 was not observed in any group. The results show that Lipiodol accumulation and retention in
38 VX2 tumor may be improved by using a monodisperse emulsion. Moreover, no significant
39 adverse events are associated with the use of the emulsion.

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42 **Introduction**

43 Transcatheter arterial chemoembolization (TACE) is a standard of care for unresectable
44 hepatocellular carcinoma (HCC), according to the Barcelona Clinic Liver Cancer (BCLC)
45 treatment protocol.[1] The procedure consists of two steps. First, a mixture of anticancer agents
46 (doxorubicin, epirubicin, cisplatin, and miriplatin) and iodized oil (Lipiodol; Guerbet,
47 Villepinte, France) is injected through microcatheters placed in a feeding artery. Gelatin slurry
48 is subsequently injected to induce ischemia. The efficacy of TACE has been validated in
49 randomized control trials.[2] There have been several attempts to further improve local tumor
50 control by using microspheres and performing balloon-occluded TACE; however, complete
51 response rates remain in the range of 26.9–57.1 %.[3–6]

52 Two types of carriers are now available for transarterial delivery of anticancer agents: Lipiodol
53 and microspheres. Well to moderately-differentiated HCC is usually fed by abnormal arteries
54 that do not accompany bile ducts (unpaired arteries) and are drained by terminal portal venules
55 or adjacent hepatic sinusoids,[7] which can be potential routes for metastasis. Lipiodol is a
56 liquid that can be distributed to the drainage area, while microspheres cannot. Therefore,
57 Lipiodol is considered a better embolization agent compared to microspheres for obtaining
58 local tumor control.

59 Unsatisfactory outcomes of TACE using Lipiodol may be due to uneven sizes of the anticancer
60 agent-Lipiodol emulsion particles. Consequently, using a monodisperse anticancer agent-
61 Lipiodol emulsion may improve local tumor control. Emulsion has been prepared by manually
62 mixing two agents using a three-way stopcock without adding a surfactant. The resultant
63 polydisperse emulsion is unstable and will typically get stuck in the proximal feeding arteries,
64 thus compromising the delivery of an anticancer agent to the tumor. A solution to this problem
65 is to use a monodisperse emulsion, which can be prepared by membrane emulsification using

66 the following procedure. A mixture of the anticancer agent and Lipiodol (water-in-oil
67 emulsion, w/o emulsion) is pushed under constant pressure through an SPG membrane (from
68 SPG Technology Co., Ltd.), which has multiple even-sized pores. A homogenous emulsion,
69 specifically a water-in-oil-in-water (w/o/w) emulsion, can then be obtained. Clinical
70 application of this type of dispersion has been already attempted using epirubicin w/o/w
71 emulsion and promising results have been obtained.[8] However, the process for preparing a
72 w/o/w emulsion is complex. Moreover, emulsions that are prepared using lipophilic anticancer
73 agents are more stable since their affinity for Lipiodol is higher than that of hydrophilic agents.
74 Miriplatin is a lipophilic platinum derivative.[9] It is prepared as a freeze-dried powder, which
75 can be readily dispersed in Lipiodol as a suspension. A solid-in-oil-in-water (s/o/w) emulsion
76 of miriplatin can be obtained by pushing a miriplatin-Lipiodol suspension through an SPG
77 membrane. The aim of the present study was to evaluate the efficacy and safety of miriplatin
78 s/o/w emulsion and compare them to those of a conventional suspension in Japanese white
79 rabbits.

80 **Materials and Methods**

81 **Preparation of conventional miriplatin suspension and miriplatin** 82 **s/o/w emulsion**

83 Miriplatin (Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan) suspension was
84 prepared using 60 mg miriplatin powder and 3 mL Lipiodol. In order to prepare the emulsion,
85 the suspension was pushed through a 20- μ m hydrophilic SPG membrane (SPG Technology
86 Co., Ltd., Miyazaki, Japan) into an outer aqueous phase using a syringe pump
87 (<https://dx.doi.org/10.17504/protocols.io.6edhba6>). PEG-60 hydrogenated castor oil (HCO 60;
88 Nikko Chemicals Co., Ltd., Tokyo, Japan) was used as a surfactant in the formulation. HCO

89 60 (0.8 %) was added to NaCl solution (0.45 %w/v) to obtain a mixture that was used as the
90 outer aqueous phase. Droplet size was measured by microscopy at 100× magnification. Kernel
91 density estimation was performed to estimate the distribution of droplet diameter.

92 **Animal experiment**

93 The study was carried out in strict accordance with the relevant guidelines and acts in
94 Japan, including the Act on Welfare and Management of Animals. The protocol was approved
95 by the Animal Experiment Ethics Committee of Nippon Medical School (Tokyo, Japan;
96 protocol number: 30-014). All efforts were made to minimize suffering. VX2-tumor-bearing
97 Japanese white rabbits (14 weeks old, clean; Japan SLC, Inc., Hamamatsu, Japan) were used
98 for the study. The tumor was implanted in the left liver lobe of each rabbit. TACE was
99 performed 14 days after tumor implantation. Five rabbits each were put in control and
100 experimental groups and administered the conventional suspension and s/o/w emulsion,
101 respectively.

102 Dynamic contrast-enhanced computed tomography (CT) scan (Aquilion PRIME; Canon
103 Medical Systems, Tochigi, Japan) was performed prior to TACE. The contrast medium
104 (iopamidol, 300 mg I/mL; Fuji Pharma Co., Ltd., Tokyo, Japan) was intravenously injected at
105 2 mL/kg at a rate of 0.2 mL/s into the animals. Quadriphasic scan was performed at 20, 40, 63,
106 and 118 s after the injection. The scanning parameters used were as follows: collimation
107 thickness, 80 × 0.5 mm; rotation speed, 0.35 s; helical pitch, 0.738; tube voltage, 80 kVp; and
108 tube current, automatic exposure control.

109 TACE was performed under general anesthesia, which was induced using a subcutaneous
110 injection of medetomidine hydrochloride (0.1 mg/kg) and ketamine hydrochloride (25 mg/kg)
111 before moving to angio suite. Anesthesia was maintained by inhalation of 2–2.5 % isoflurane
112 in angio suite. Each rabbit was monitored during the procedure using an electrocardiograph

113 and a pulse oximeter. The common femoral artery was surgically exposed, into which a 4-F
114 introducer sheath (Medikit Co., Ltd., Tokyo, Japan) was inserted. The celiac artery was
115 cannulated with a 4-F C2 diagnostic catheter (Medikit Co., Ltd.). Next, a 2-F microcatheter
116 (Gold Crest Neo; HI-LEX, Takarazuka, Japan) was coaxially advanced into the left hepatic
117 artery, after which 0.1 mL of either the suspension or emulsion was injected under fluoroscopic
118 guidance. A plain CT scan was taken immediately after the procedure.

119 All the rabbits were euthanized two days after TACE by injecting pentobarbital sodium
120 (100mg/kg) intravenously. Dynamic contrast-enhanced CT scanning was performed prior to
121 sacrifice by following the same protocol as before TACE. The tumor was extracted and cut in
122 half: one half was used for pathological evaluation, whereas the other half was evaluated for
123 its iodine content by mass spectroscopy.

124 **Evaluation of the efficacy of the emulsion**

125 Accumulation of iodized oil in the tumors was assessed by mass spectroscopy (for
126 iodine concentration) as well as pathological and radiological analyses.

127 **Mass spectroscopy**

128 Iodine concentration in the specimens was evaluated by inductively-coupled plasma
129 mass spectroscopy (Japan Testing Laboratories, Inc., Ogaki, Japan). Median iodine
130 concentration was then compared between the two animal groups.

131 **Pathological evaluation**

132 Oil red O staining, which is a lipid staining test, was performed to quantitatively
133 evaluate the accumulation of iodized oil in the tumors. Each specimen was prepared using the
134 maximum cross-section of the tumor. Digitization was done by whole slide imaging
135 (NanoZoomer-XR; Hamamatsu Photonics K.K., Yokohama, Japan). Each scanned image was

136 compressed to obtain a JPEG image with a resolution of 1920×984 pixels. Lipiodol
137 accumulation was evaluated using the HSV model, which defines color space by three
138 parameters: hue, saturation, and value. Lesions without lipid were bluish in color. An area with
139 a 'hue' value of more than 55 and less than 65 was digitally subtracted from the digitized
140 specimen by setting 'value' to be zero. The remaining area was considered to be the region of
141 Lipiodol accumulation. The extent of Lipiodol accumulation was evaluated using 'saturation'.
142 Source codes were written in Python (Anaconda 4.6.14; Anaconda, Inc., Austin, TX, USA)
143 using Jupyter Notebook, whereas cv2 module was used for image processing as described
144 above.

145 **Radiological evaluation**

146 A slice of specimen was selected to include the maximum cross-section of the tumor
147 for the evaluation. A region of interest (ROI) was defined to cover the target tumor in the CT
148 images taken before, immediately after (POD 0), and two days after (POD 2) TACE. Mean
149 Hounsfield unit (HU) values were used for the evaluation. Washout rate was defined as the
150 difference in HU values between POD 0 and POD 2, divided by the HU value for POD 0.

151 **Evaluation of adverse events**

152 Cholecystitis, bile duct injury, and biloma formation were considered as potential
153 adverse events. The extent of Lipiodol accumulation in the gallbladder was evaluated using CT
154 images, whereas inflammation of the gallbladder was evaluated using pathological specimens.
155 Bile duct injury and biloma formation were pathologically evaluated.

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158 Results

159 A monodisperse s/o/w emulsion containing miriplatin was successfully formulated with
160 a mean diameter of $62.0 \pm 6.42 \mu\text{m}$ (Fig 1). Kernel density estimation showed that the mode
161 droplet size was $60.0 \mu\text{m}$. All experimental procedures were successfully performed.

162 The mean body weights of the rabbits were 2.6 ± 0.1 and 2.7 ± 0.1 kg in the control and
163 experimental groups, respectively. Tumor diameter was 14.3 ± 5.6 mm in the control group
164 and 15.4 ± 3.0 mm in the experimental group. All tumors were confirmed to be in the left lobe
165 by CT scan prior to performing TACE.

166 **Fig 1. The s/o/w miriplatin emulsion.** (A) Image of s/o/w miriplatin emulsion (as obtained
167 from the microscopic analysis) ($100\times$ magnification). (B) Results of kernel density estimation.
168 The data was calculated based on droplet diameters obtained from the microscopic analysis.

169
170 Median iodine concentration was higher in the experimental group (1100 ppm, range: 750–
171 1500 ppm) than in the control group (840 ppm, range: 660–1800 ppm (Fig 2). The median
172 saturation was also higher in the experimental group (4.4, range: 2.8–20.3) than in the control
173 group (3.8, range: 2.1–8.1) (Fig 3). Mean HU value was higher in the experimental group than
174 in the control group immediately after TACE [199.6 (134.0–301.7) vs. 165.3 (131.4–280.5)]
175 as well as two days after TACE [114.2 (56.1–229.8) vs. 58.3 (42.9–132.5)] (Fig 4). Washout
176 rate was higher in the control group [55.6 (51.1–75.4)] than in the experimental group [49.9
177 (23.8–58.1)] (Fig 4). Lipiodol accumulation varied greatly even among animals in the same
178 group. Extensive Lipiodol deposition was observed in all but one rabbit in the experimental
179 group (Figs 5 and 6). Poor Lipiodol deposition was possibly due to a massive arterioportal
180 shunt around the tumors. Lipiodol tended to deposit in normal liver parenchyma rather than in

181 the tumors, as observed in the pathological specimens and CT images (Fig 6). A low-density
182 area was observed at the interface between the tumor and the normal liver parenchyma, which
183 possibly indicates liquefying necrosis, in all the rabbits in the experimental group and in three
184 rabbits in the control group (Figs 5 and 6).

185 **Fig 2. Iodine concentration in the tumors.** The concentration of iodine (ppm) in the tumors
186 was evaluated by inductively-coupled plasma mass spectroscopy.

187 **Fig 3. Quantitative pathological evaluation of Lipiodol accumulation in the tumors.** The
188 HSV model was used in the assessment. ‘Saturation’ values for areas with Lipiodol
189 accumulation were evaluated using digitized specimens stained with Oil red O.

190 **Fig 4. Radiological evaluation of Lipiodol accumulation in the tumors.** Mean HU value (A)
191 immediately after and (B) two days after TACE. (C) Lipiodol washout rate.

192 **Fig 5. Representative images showing Lipiodol deposition.** (A–C) Images for a rabbit in the
193 experimental group. The s/o/w miriplatin emulsion was injected via the left hepatic artery. (C)
194 Dense Lipiodol accumulation observed two days after TACE (white arrow). (D–F) Images for
195 a rabbit in the control group. Miriplatin suspension was injected via the left hepatic artery. (F)
196 Slight accumulation of Lipiodol observed two days after TACE (white dashed arrow).

197 **Fig 6. Representative images showing poor Lipiodol accumulation in a rabbit in the**
198 **experimental group.** (A) A massive arterioportal shunt around the tumor (white arrow). (B)
199 Lipiodol accumulation higher in the liver parenchyma than in the tumor immediately after
200 TACE (white dashed arrow). (C) Necrosis in liver parenchyma surrounding the tumor two days
201 after TACE (white arrowhead). (D) Lipiodol accumulation in normal liver parenchyma in
202 specimen stained with Oil red O (black arrow).

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204 In the experimental group, Lipiodol accumulation in the gallbladder was observed in four
205 rabbits immediately after TACE; however, washout was observed in all rabbits and
206 cholecystitis was not observed. Conversely, in the control group, Lipiodol accumulation was
207 observed in three rabbits after TACE and washout was not observed in one animal, in which
208 cholecystitis ensued (Fig 7). Bile duct injury and biloma were not observed in either group.

209 **Fig 7. A case of cholecystitis following TACE.** (A) Diffuse Lipiodol accumulation in the
210 gallbladder wall, as observed in a CT scan, immediately after TACE (white arrow). (B)
211 Lipiodol retention in the gallbladder wall, as well as thickening of the wall, two days after
212 TACE (white dashed arrow). (C) Infiltration of inflammatory cells into the gallbladder wall,
213 which is indicative of cholecystitis (black arrowheads).

214 Discussion

215 Improved accumulation of Lipiodol in the VX2 tumors was observed using the novel
216 s/o/w miriplatin emulsion, compared to the conventional miriplatin suspension. It is considered
217 that Lipiodol distribution to the tumor was improved because a monodisperse emulsion was
218 used. This was verified by performing mass spectroscopy, radiological, and pathological
219 analyses. Miriplatin is a lipophilic platinum derivative, which was specially designed to have
220 an increased affinity for Lipiodol. Therefore, it can be well dispersed in Lipiodol to form an
221 aqueous suspension and gradually release active platinum into the aqueous phase.[10]
222 Miriplatin has several advantages over other anticancer drugs such as doxorubicin, epirubicin,
223 cisplatin, and mitomycin C. Anticancer agents are usually prepared as emulsions by manually
224 mixing them with Lipiodol using a three-way stopcock without adding a surfactant. This yields
225 a relatively unstable emulsion since a surfactant is required to stabilize the system. Body
226 temperature may also facilitate aggregation of the emulsion, causing its breakdown in the blood
227 stream after injection into the body. Once the emulsion breaks down, the anticancer agent and

228 Lipiodol reach the tumor microcirculation as separate components, which does not allow
229 Lipiodol to work as an efficient carrier. Miriplatin may be superior to other agents since it will
230 be delivered to the tumor combined to Lipiodol. Moreover, compared to epirubicin or cisplatin,
231 miriplatin induces lesser vascular damage.[11,12] TACE is indicated for BCLC intermediate
232 stage, which is typically characterized by multiple lesions that require repeated treatment. It is
233 reported that anticancer agents can cause arterial damage when injected into the hepatic artery.
234 Additionally, they can cause occlusion of the vessel or arterioportal shunt. This compromises
235 drug delivery following TACE sessions and may lead to insufficient drug accumulation in the
236 tumor. Miriplatin may be thus suitable for repeated TACE.

237 The results of a previous randomized control trial showed that the antitumor effect of miriplatin
238 is equal or superior to that of epirubicin or cisplatin. However, it is also reported that
239 administering miriplatin as a high-viscosity formulation or large-droplet suspension may
240 impede its delivery.[13–15] One solution to this problem is to use warmed miriplatin because
241 the viscosity of miriplatin decreases on warming.[16] It has been demonstrated in some clinical
242 studies that miriplatin shows a higher efficacy and improves tumor control better when it is
243 warmed; however, local tumor control rate remains unsatisfactorily low (objective response
244 rate: 40–46.7 %).[17,18] Moreover, the temperature of administered miriplatin suspension
245 decreases along the way to the tumor, which attenuates the warming effect.

246 Another solution is to emulsify the miriplatin suspension. The droplet sizes of miriplatin
247 suspensions vary, and occlusion of the feeding vessel can occur when large droplets are stacked
248 in the proximal hepatic artery before optimal accumulation of the suspension is achieved.[15]
249 This problem can be solved by using a monodisperse emulsion. Optimal accumulation of the
250 emulsion can be obtained by carefully setting the droplet size of the emulsion to be less than
251 the diameter of feeding arteries. The emulsion can also be stabilized by adding surfactant to
252 the formulation. The results of the present study showed better Lipiodol accumulation in the

253 tumors, both immediately after and two days after TACE, with the s/o/w emulsion than with
254 the conventional suspension. Lipiodol retention in the tumors was also better with the s/o/w
255 emulsion, which possibly reflects the stable nature of the emulsion. Moreover, necrosis of the
256 tumor-normal parenchymal interface was more common in the experimental group. Local
257 tumor recurrence tended to occur in the lesions and a sufficient margin is essential for tumor
258 control when performing TACE.[19] Therefore, local tumor recurrence may be reduced by
259 using the s/o/w emulsion.

260 No significant adverse events were observed in the experimental group; however, cholecystitis
261 was observed in one rabbit in the control group. Lipiodol accumulation in the gallbladder wall
262 was more common immediately after TACE in the experimental group; however, washout was
263 observed in all rabbits in the group two days after the procedure. This may due to the stability
264 and uniform droplet size of the emulsion. This is because if the emulsion is unstable, it can
265 break down inside the arteries feeding normal structures. This will result in exposure of blood
266 vessels to the anticancer drug, which may cause vascular injury. Ischemic injury may also occur
267 if large Lipiodol droplets block proximal arteries; however, this is less likely to occur with the
268 s/o/w emulsion than with the conventional suspension. Ischemic bile duct injury, which is a
269 major complication and drawback of TACE, was not observed in this study. This indicates that
270 the monodisperse s/o/w emulsion may be a safer alternative to the conventional suspension.

271 Promising results were obtained in the present study; however, a few clarifications are needed.
272 Firstly, differences in the antitumor effects of the s/o/w emulsion and the conventional
273 suspension are unclear. This is because the amounts of miriplatin and Lipiodol in the
274 administered doses were lower than the required amounts for complete tumor necrosis. This
275 was done to notice differences in Lipiodol accumulation in the tumors more clearly. Thus, the
276 extent of necrosis should be evaluated in further studies after the full doses of the two
277 ingredients are administered to both groups of rabbits. Additionally, the two-day period from

278 TACE to animal sacrifice was too short for effective evaluation of antitumor effect. It has been
279 shown that, in VX2-tumor-bearing rabbits, the difference in the concentration of an anticancer
280 agent between the tumor and normal liver parenchyma peaks in approximately three days after
281 TACE is performed when an emulsion prepared using SPG membrane is administered to the
282 rabbits.[20] The main purpose of the present study was to evaluate the difference in Lipiodol
283 distribution following treatment with conventional miriplatin suspension or miriplatin s/o/w
284 emulsion. Thus, the observational period in future experiments should be longer. Furthermore,
285 the droplet size of the emulsion should be considered. For instance, in the present study, an
286 SPG membrane with a pore size of 20 μm was used to obtain an emulsion with a peak droplet
287 diameter of 60 μm . This was because a previous clinical study on the efficacy of an epirubicin
288 w/o/w emulsion revealed that local tumor control was better when droplet size 70 μm than
289 when it was 30 μm .[21] Emulsions with small-sized droplets can enter microcirculation
290 without being trapped, which indicates that droplet sizes as large as 70 μm are recommended.
291 However, the data on the vessel diameters of rabbits are scarce and optimal target droplet size
292 for rabbits should be determined by further investigation.

293 In conclusion, Lipiodol accumulation and retention in VX2 tumor may be improved by using
294 a monodisperse emulsion, which is associated with no significant adverse events.

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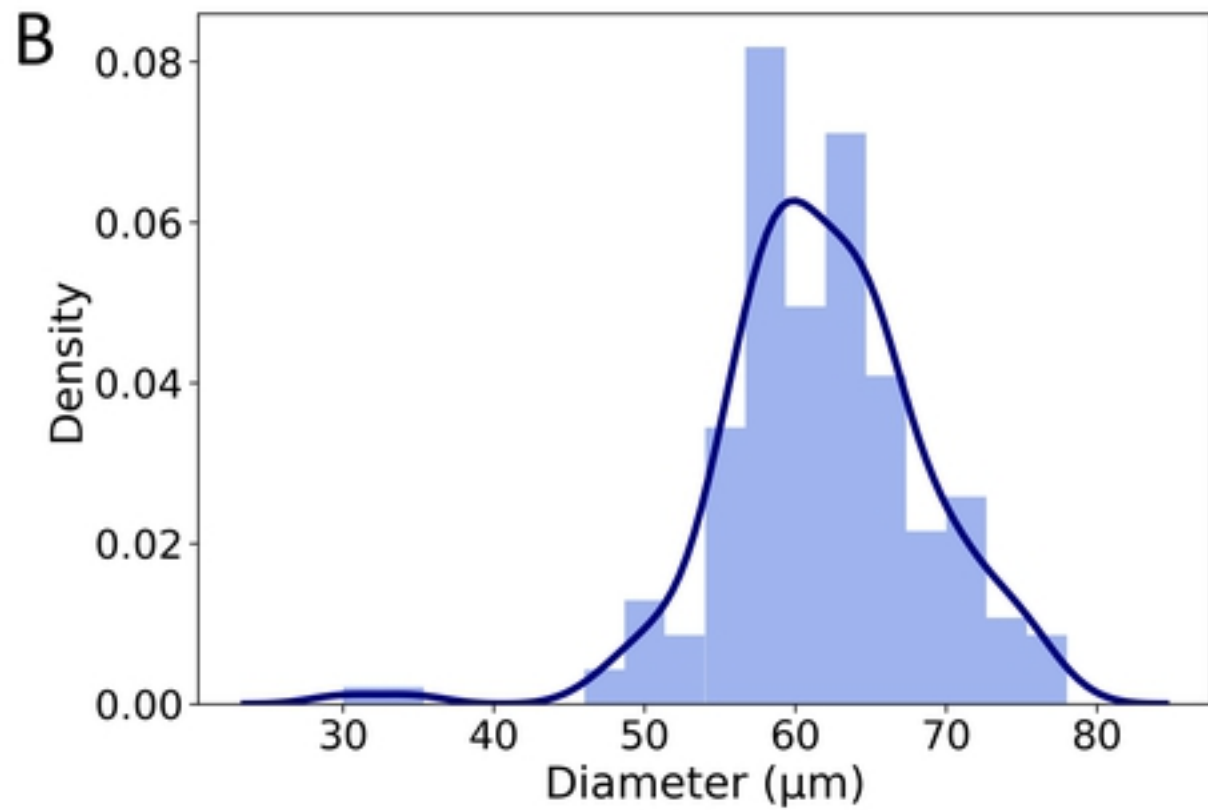
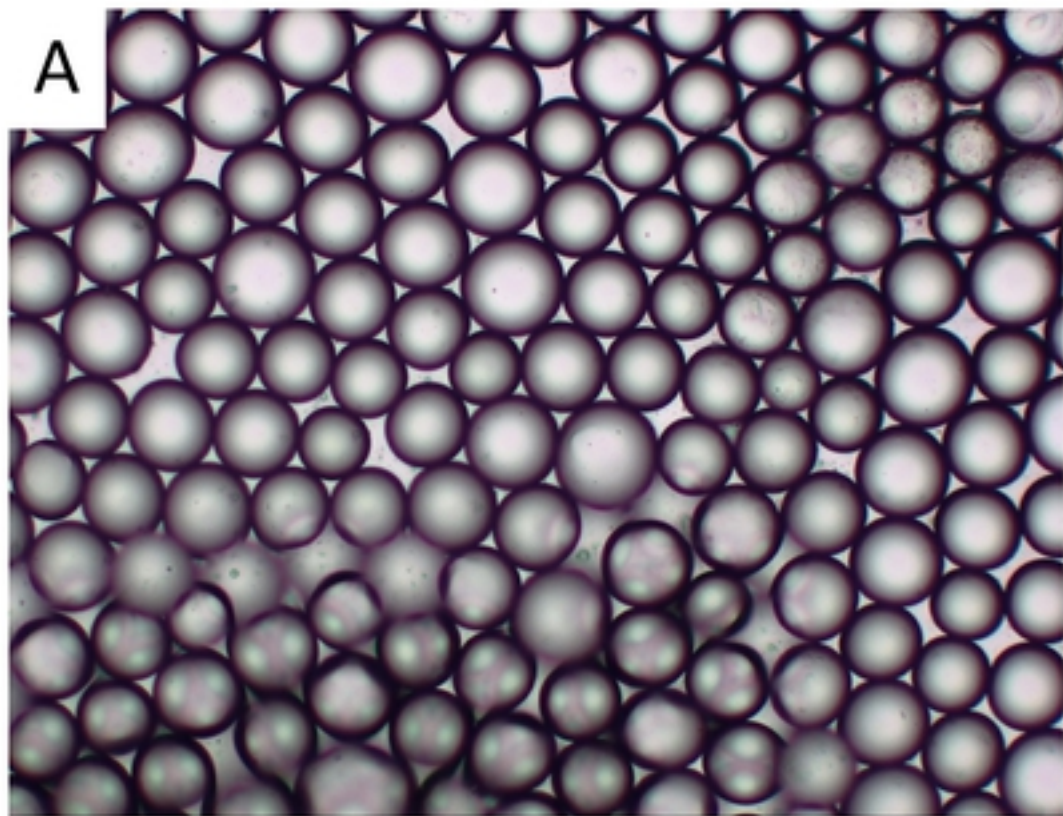
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387 **Supporting information captions**

388 **S1 Video. Injection of s/o/w emulsion.**

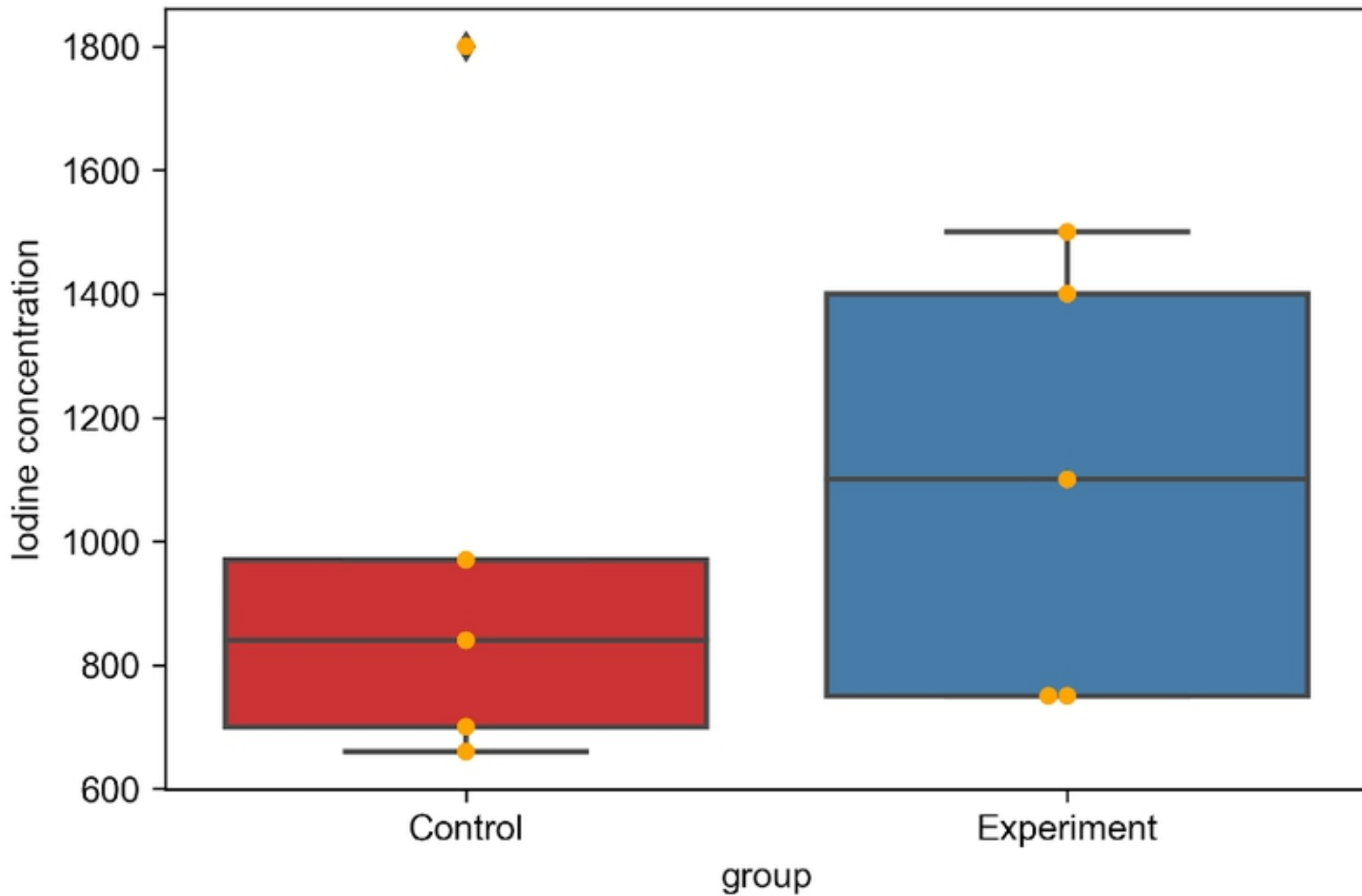
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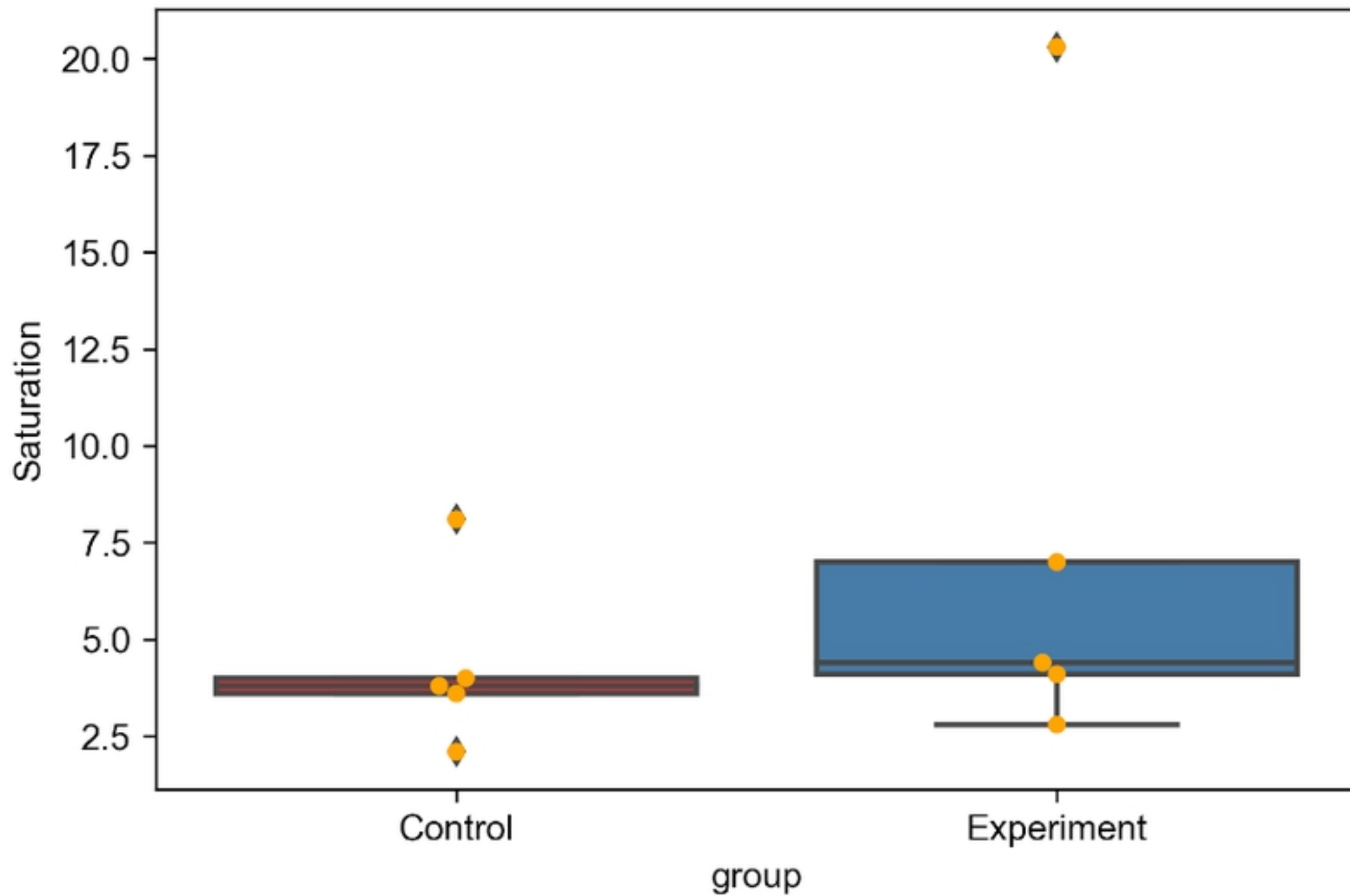
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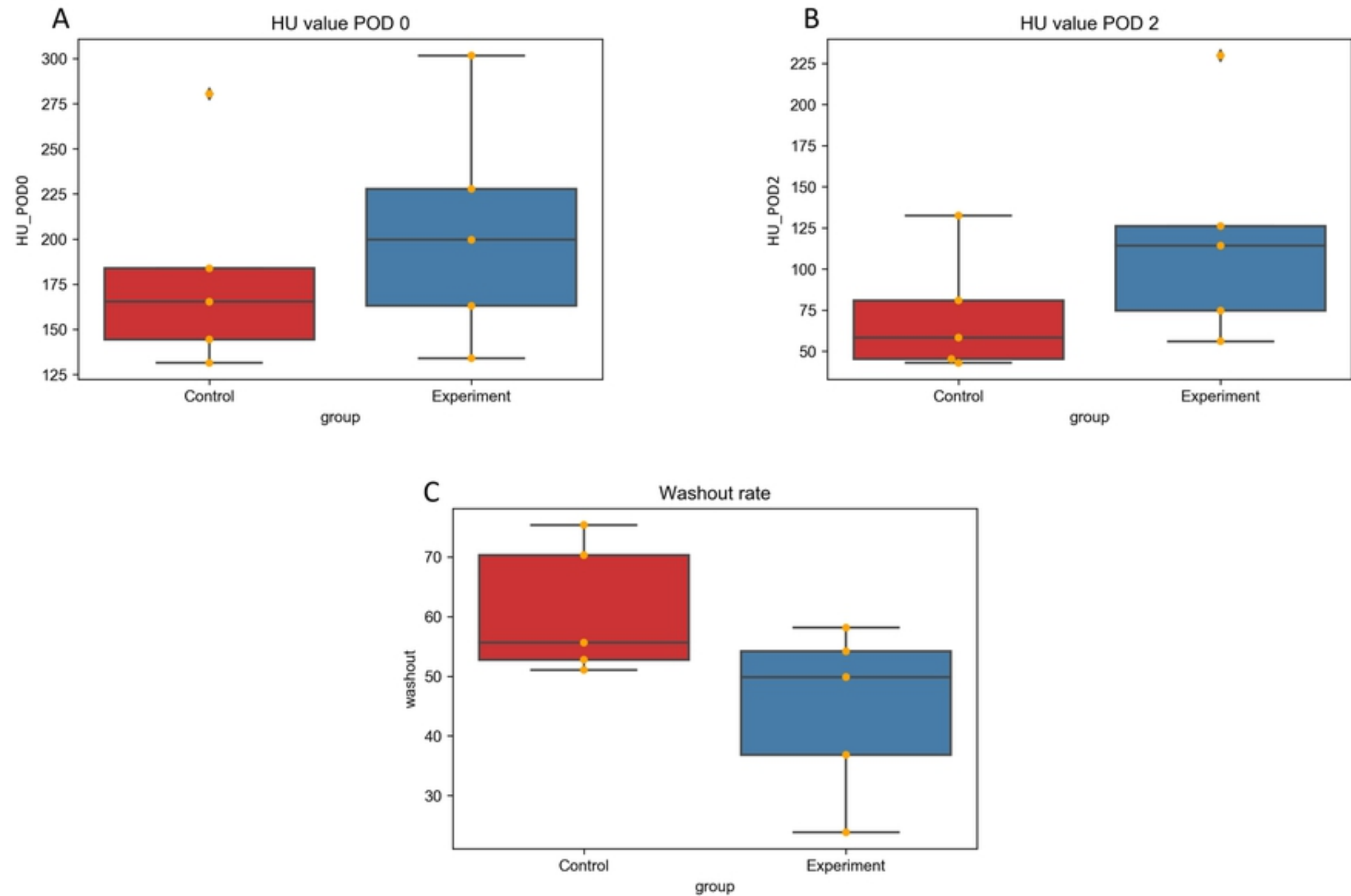


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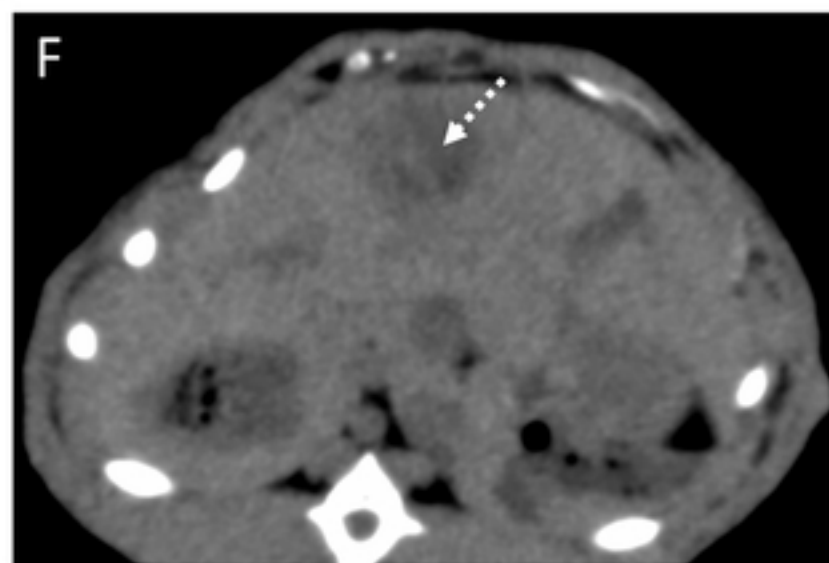
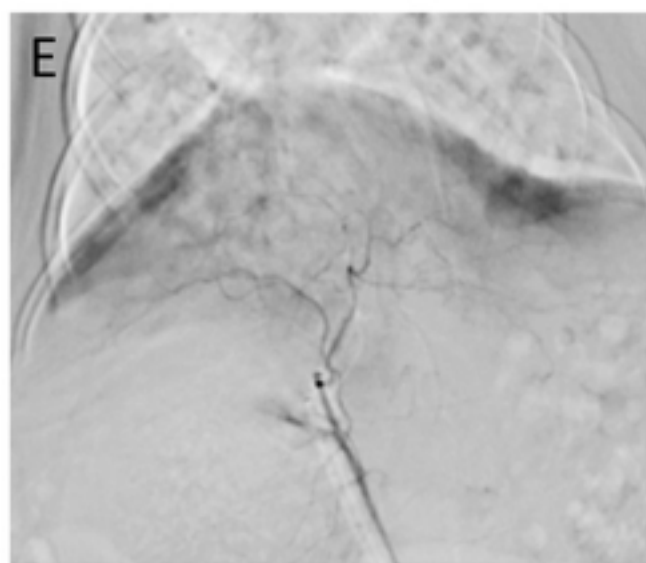
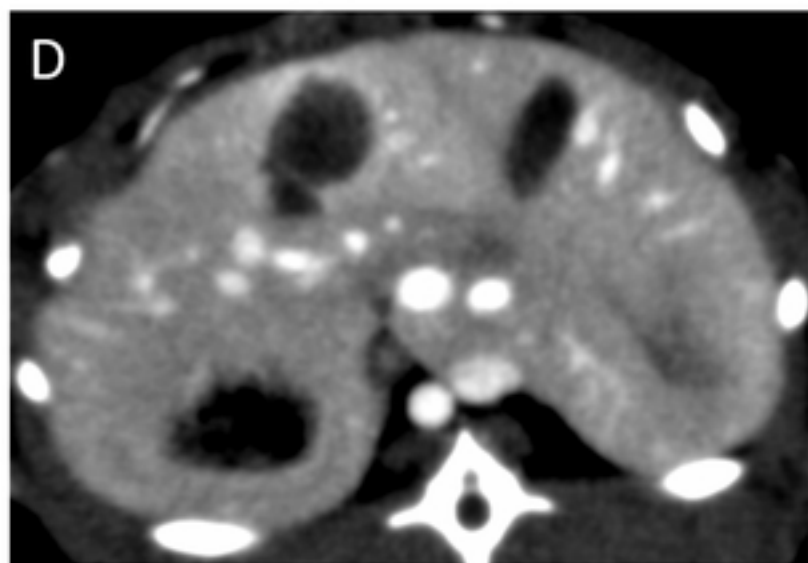
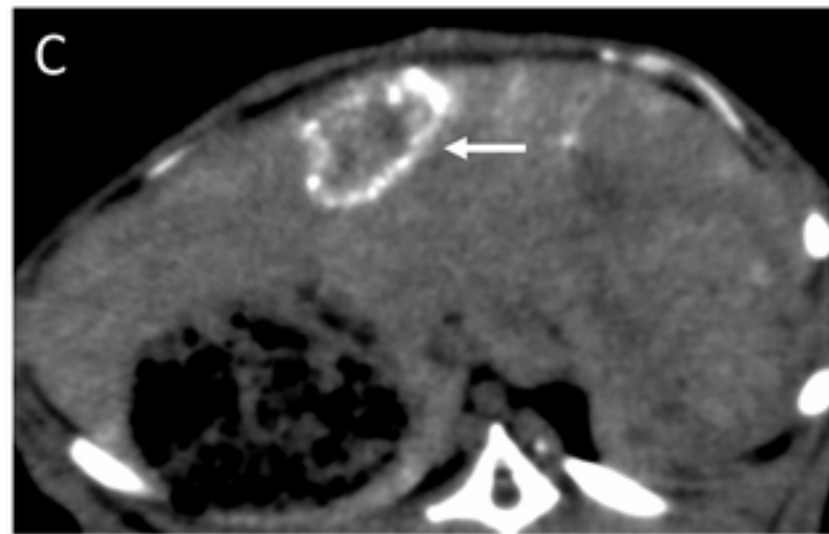
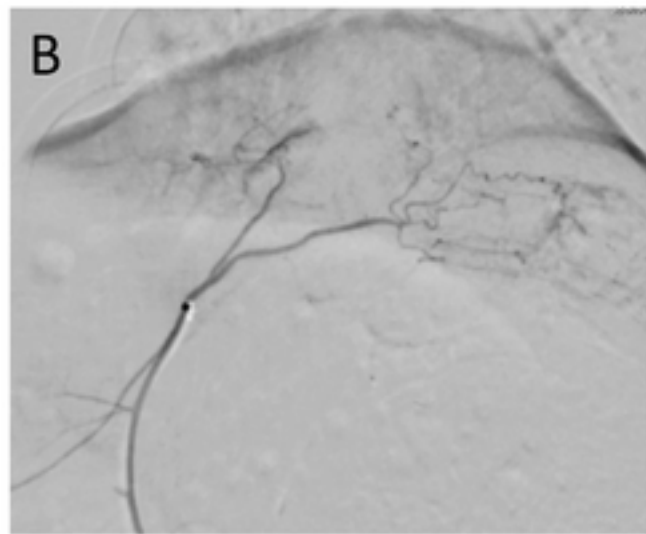
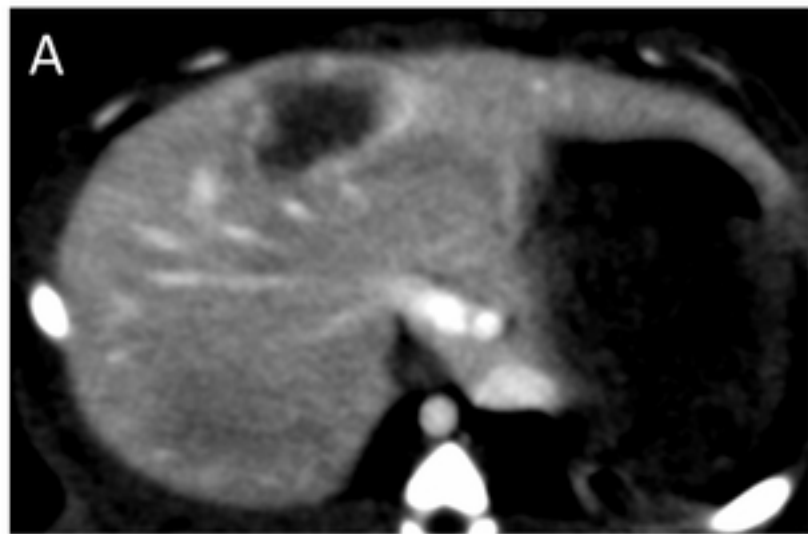
Pathological evaluation



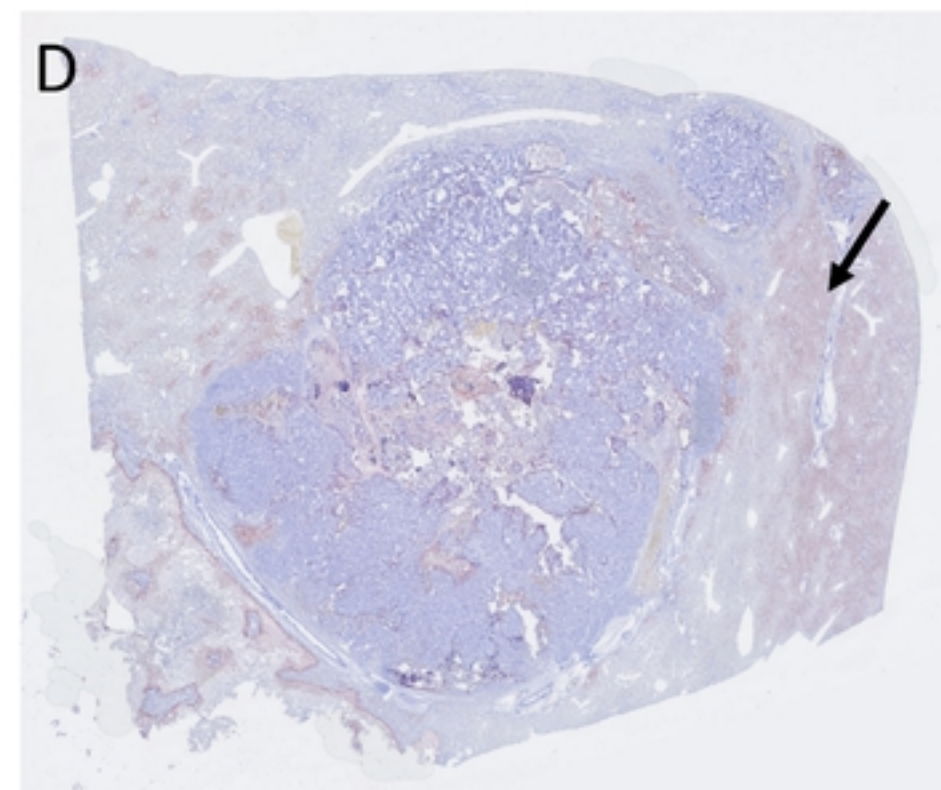
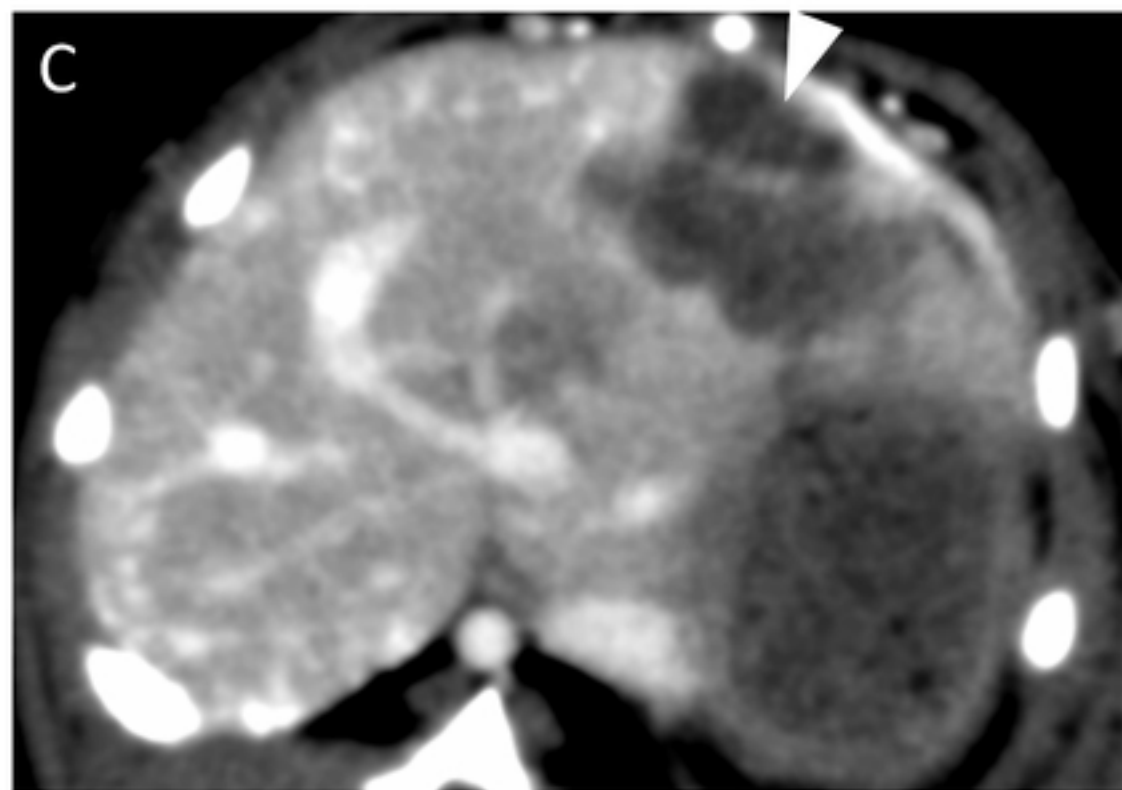
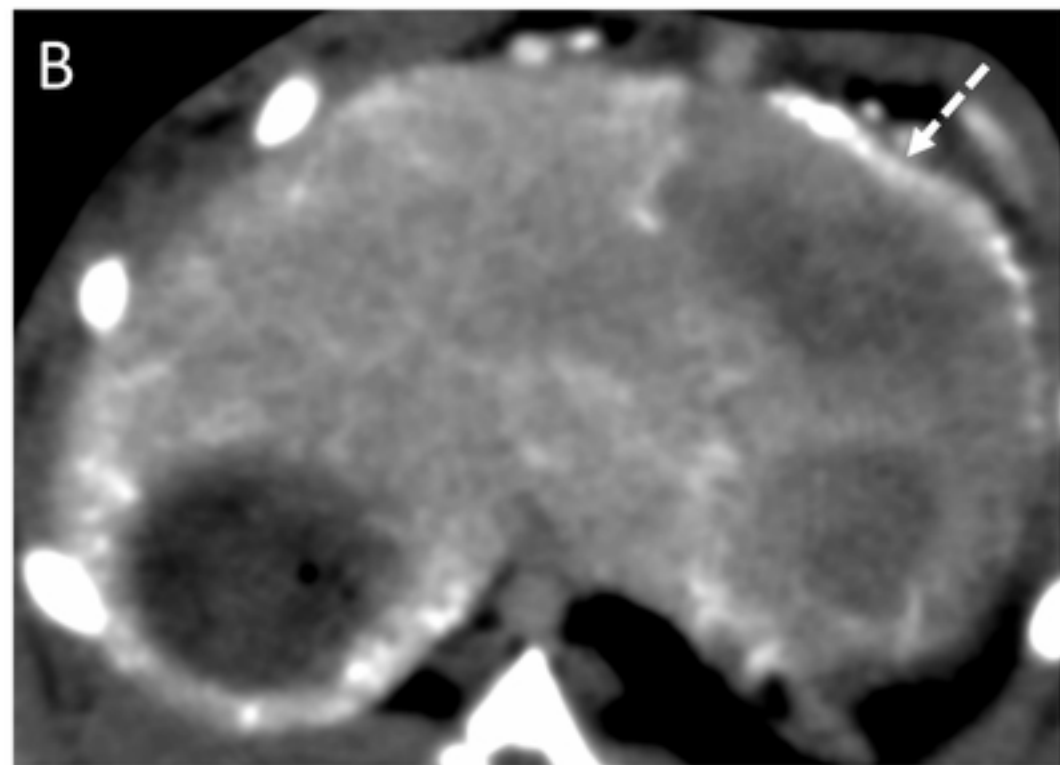
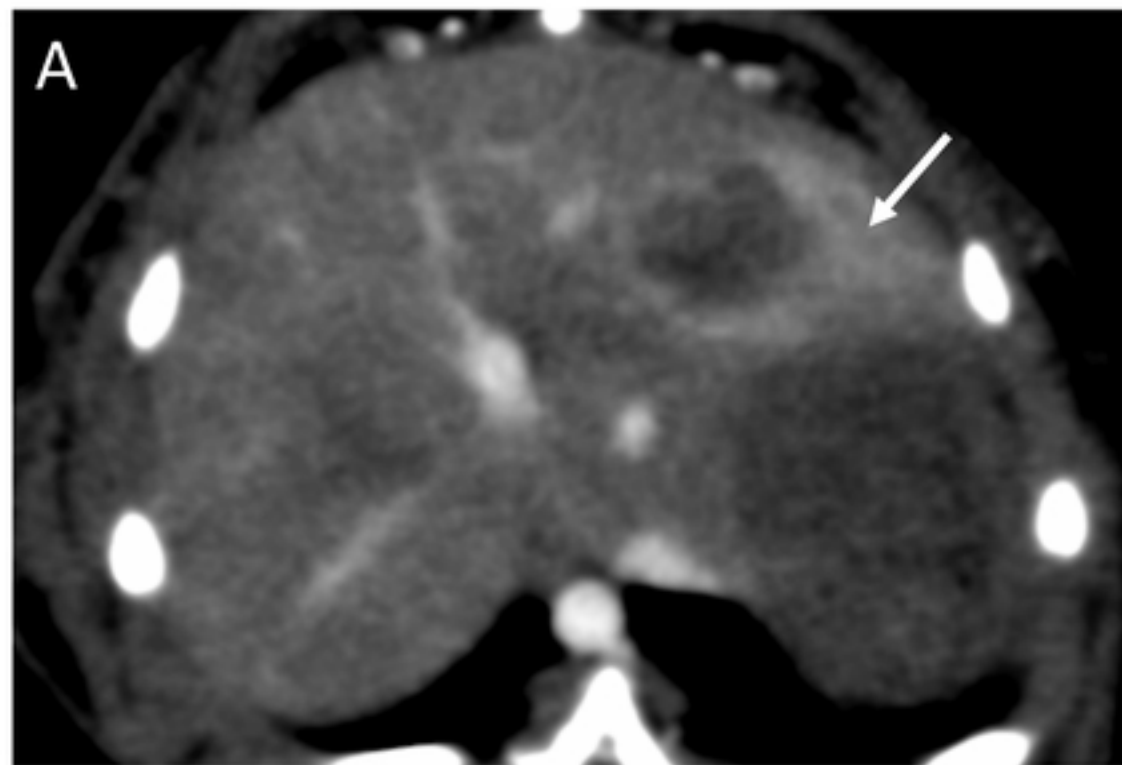
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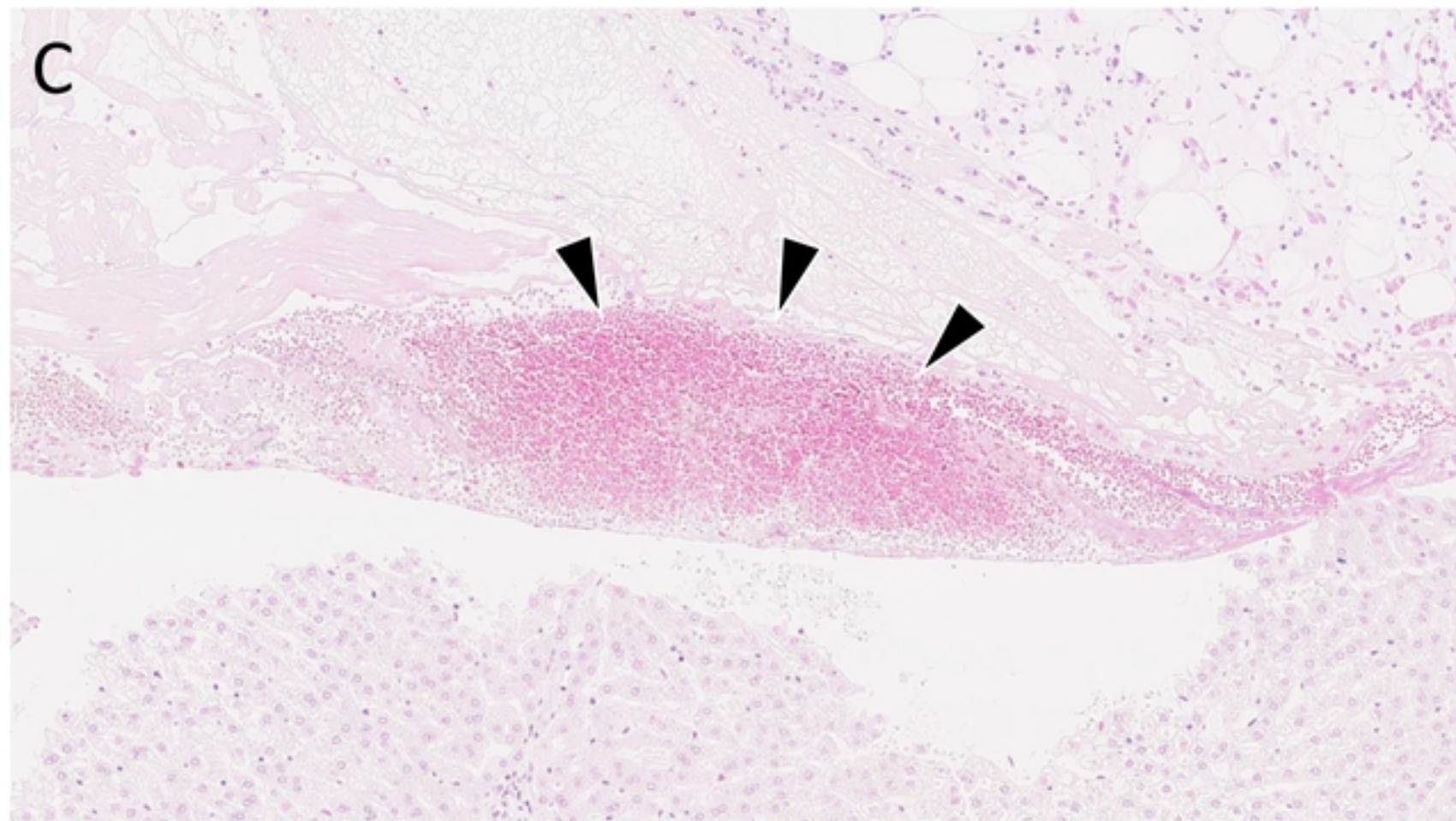
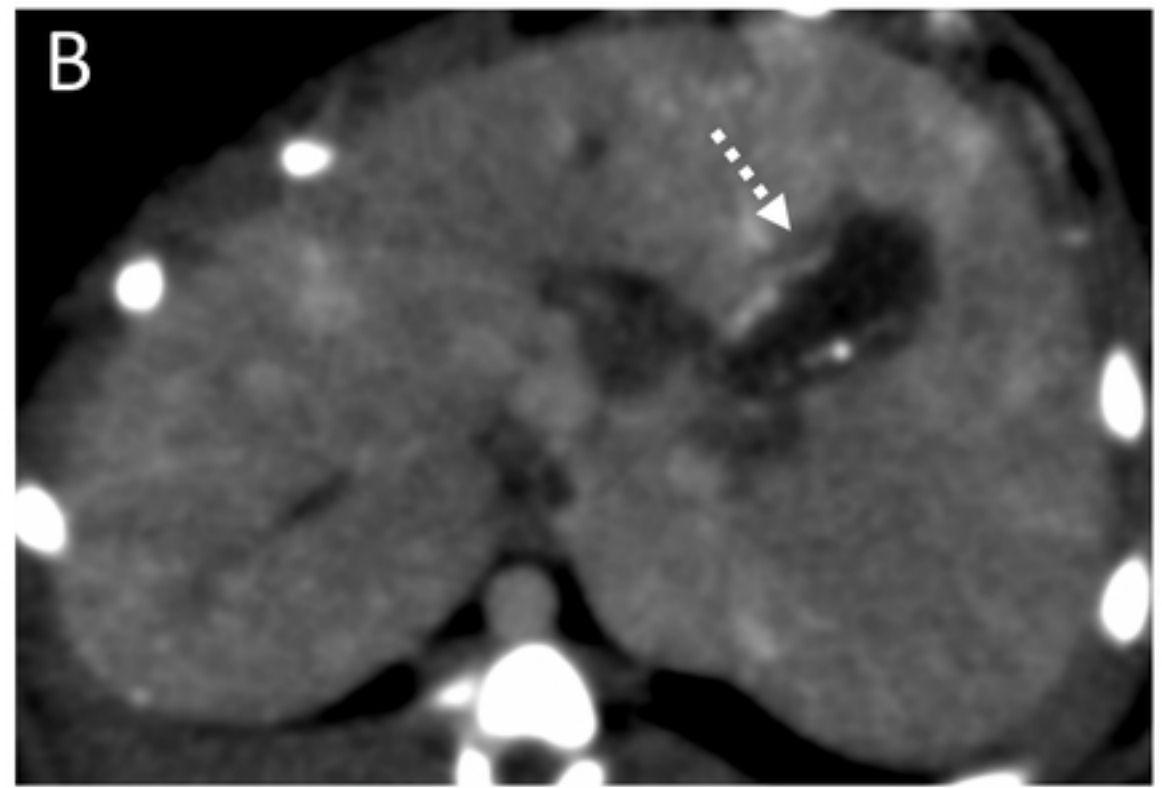
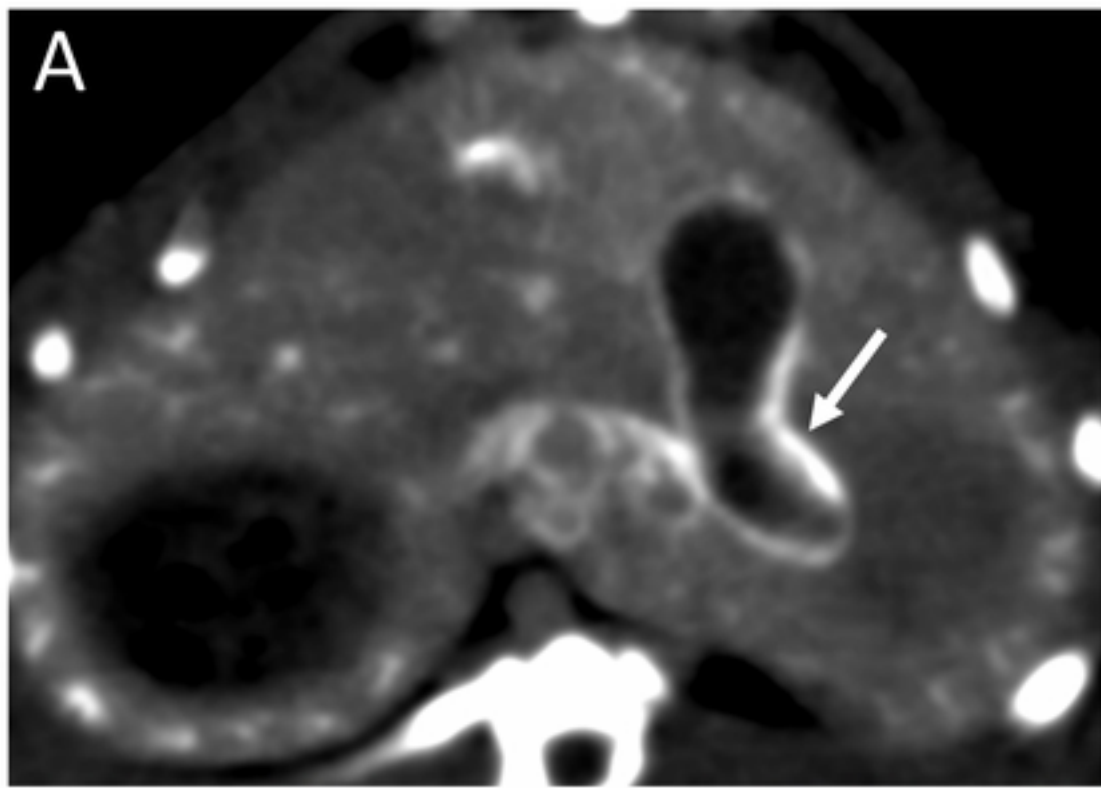
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