

# The role of amyloid PET in patient selection for extra-ventricular shunt insertion for the treatment of idiopathic normal pressure hydrocephalus: a pooled analysis

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## Research

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## Abstract

Idiopathic Normal Pressure Hydrocephalus (iNPH) can be effectively treated through shunt insertion. However, most shunted patients experience little or no clinical benefit, which suggests suboptimal patient selection. While contentious, multiple studies have reported poorer shunt outcomes associated with concomitant Alzheimer's disease. Prompted by this observation, multiple studies have assessed the role of amyloid PET, a specific test for Alzheimer's disease, in patient selection for shunting.

Across three relevant studies, a total of 38 patients with suspected iNPH underwent amyloid PET imaging and shunt insertion. Twenty-one patients had a positive clinical response to shunting. 18/28 (64.3%) of patients with a negative amyloid PET and 5/10 (50%) with a positive amyloid PET had a positive response to shunting. The pooled sensitivity, specificity and accuracy was 33.3%, 76.2% and 58.3%. None of these statistics reached statistical significance.

The results of this pooled analysis do not support the selection of patients with suspected iNPH for shunting on the basis of amyloid PET alone. However, due to small cohort sizes and weakness in study design, further high-quality studies are required to properly determine the role of amyloid PET in assessing this complex patient group.

## Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a communicating hydrocephalus that causes a progressive syndrome typified by cognitive impairment, gait apraxia and urinary incontinence [1]. Ventriculomegaly develops despite normal CSF opening pressure on lumbar puncture. Disruption of normal CSF dynamics [2, 3], ciliary dysfunction [4], accumulation of toxic metabolites [5], reduced glymphatic drainage [6], and impaired cerebrovascular autoregulation [7], have all been implicated, but the pathogenesis of iNPH remains poorly understood.

Unlike most other causes of dementia which have no disease modifying treatment, iNPH can improve with CSF diversion [1]. Accurate patient selection is important due to the risk of serious complications. Haemorrhage, infection, over-drainage, obstruction and device failure occurs in 38% of patients [8, 9]. Permanent neurological sequelae or death occurs in 6% of patients [10].

Despite ongoing refinement of the iNPH diagnostic guidelines [11–15] and imaging criteria [16], patient selection is suboptimal. As few as 28% of patients improve after shunting mainly due to the overlap in the clinical and imaging features of iNPH with other conditions, such as Alzheimer's disease (AD) and progressive supranuclear palsy [17], that are not treated with shunting.

The implications of AD pathology based on cortical biopsy or CSF analysis is contentious. Evidence of comorbid AD has been associated with poorer [18–22], similar [23, 24] and better [25] outcomes following CSF drainage. The discrepancy between these studies may be related to the biopsy of unrepresentative cerebral cortex or the reduced reliability of CSF analysis in patients with iNPH where toxic metabolic clearance is impaired [26].

There remains an unmet need for a non-invasive method of accurately identifying patients with shunt-responsive iNPH. Multiple structural imaging features are associated with shunt responsiveness [16, 27–31], however they are non-specific when considered in isolation. Increasingly complex MRI techniques have been used to augment patient selection for shunting, including Sylvian aqueduct CSF flow dynamics [32], dynamic contrast enhancement [33], water molecule diffusivity [34, 35], elastography [36] and spectroscopy [37, 38], however none have been validated for routine clinical use.

The role of PET imaging in neurodegenerative disease has expanded massively [39–41]. For the assessment of AD, multiple radiotracers have been developed that cross the blood brain barrier to bind specifically to A $\beta$  [42]. AD can be reliably excluded by a normal uptake pattern of <sup>11</sup>C-Pittsburgh Compound B (PiB), <sup>18</sup>F-florbetapir (Amyvid) [43], <sup>18</sup>F-flutemetamol (Vizamyl) [44], and <sup>18</sup>F-florbetaben (Neuraceq) [45] (Figure 1).

Working on the hypothesis that amyloid deposition is associated with AD, which is associated with a poor response to shunting, multiple studies have examined the association between amyloid PET and clinical outcomes following shunt insertion in patients with suspected iNPH. In this article we present a pooled analysis of their results.

## Methods

### Study identification

A comprehensive search was performed for human studies published in the English language between 1st January 1990 and 1st September 2020 through electronic databases including MEDLINE, Embase, and Web of Science. A combination of keywords and MeSH terms were used, specifically "normal pressure hydrocephalus", "NPH", "iNPH", "Alzheimer's Disease", "AD", "amyloid", "amyloid PET", "amyloid radiotracer", "CSF diversion", "CSF tap test", "extended lumbar drain", "shunt surgery" and "shunt response".

### Inclusion and exclusion criteria

Studies were included if they reported the association between amyloid PET imaging findings and the response to a shunt in patients with suspected iNPH.

Studies were excluded if amyloid imaging was performed after shunting, if the decision to shunt was based on the amyloid PET result or if individual patient outcomes were not reported.

## Data extraction

Data extraction was performed independently by two readers with adjudication by a third, if necessary.

## Statistical analysis

Results from individual studies were combined to pool estimates of sensitivity, specificity, negative predictive value, positive predictive value, and accuracy. Diagnostic statistics are presented as a percentage alongside the 95% confidence interval calculated using the Clopper-Pearson method. Numerical data are presented as a mean with the standard deviation, unless otherwise specified. Statistics were calculated using the statsmodels (version 0.12) package in Python 3.7.

## Results

Three studies were identified that compared the clinical response to shunting between those with and without a positive amyloid PET scan [46–48].

Two further studies of amyloid PET performed before shunting were found but were excluded as the response to shunting was not reported [49, 50]. Additionally, both studies included patients from the same group and registry as one of the three studies that was already included. No detail was provided on any overlap in patient cohorts between these studies.

In a sixth study by Jang *et al* [51], the primary outcome was the association between CSF tap test and amyloid PET results. As only patients with a negative amyloid PET were offered a shunt, the study was excluded.

Details of the three studies that were included in the pooled analysis are provided in Table 1. The association between amyloid PET imaging and shunt response was the primary study outcome in a study by Hiraoka *et al*, whereas it was a secondary outcome in the other studies. Patients were recruited between approximately 2007 and 2016. In the study by Rinne *et al*, the recruitment period was not provided. Across all studies, 38 patients were shunted.

The technical detail of PET imaging including the choice of radiotracer is provided in Table 2. <sup>18</sup>F-flutemetamol was used in two studies and <sup>11</sup>C-BF227 in one study.

Of the 38 patients shunted and followed-up, 23 had a positive clinical response. 18/28 (64.3%) and 5/10 (50%) of patients with a negative amyloid PET and positive amyloid PET had a positive response to shunting, respectively. The Fisher's exact test *P* value for the association between shunt response and amyloid PET result was 0.473.

The diagnostic statistics for the prediction of a shunt response in those with a negative amyloid PET is provided in Table 3. Sensitivity, specificity and accuracy ranged from 0–60.0%, 60.0–87.5% and 52.9–72.7%, respectively. The respective pooled sensitivity, specificity and accuracy was 33.3%, 78.3% and 60.5%.

All three studies reported the SUVR (Standardised Uptake Value Ratio) for each patient, which are provided in Supplementary Table 1. The box and whisker plot in Figure 2 shows that SUVRs are generally higher in those who did not respond to shunting than those who did respond to shunting, although, neither individually nor when pooled, was the difference statistically significant.

Amyloid PET was well tolerated with only two cases of minor adverse reactions (nausea) reported by Rinne *et al* and four minor adverse reactions (dizziness, headache, abdominal pain, and throat irritation) by Leinonen *et al*. Hiraoka *et al* did not discuss adverse reactions.

## Discussion

iNPH can be effectively treated through shunt insertion [52]. However, as many patients who undergo this procedure experience short-lived or no benefit from the procedure, patient selection is suboptimal. Prompted by reports of better shunt outcomes in those without evidence of AD [20, 53, 54], multiple studies have sought to determine how amyloid PET could improve patient selection. We present a pooled analysis of three non-randomised studies that have examined the association between amyloid PET and the clinical response to shunt insertion.

## Association between amyloid PET and shunt response

The pooled results of the three studies shows low sensitivity (33.3%) and a moderate specificity (78.3%) in identifying patients with a poor response to shunting. Proportionally more patients who responded to a shunt had a negative amyloid PET than a positive amyloid PET (61.5% versus 50%), although the difference was not statistically significant. Therefore, the main finding in this pooled analysis is that amyloid PET, when considered in isolation, does not accurately identify patients with suspected iNPH who are likely to respond to shunting.

## Weaknesses of included studies

There are multiple inherent weaknesses within the studies included in this pooled analysis.

All of the studies were non-randomised and therefore inherit all of the limitations of such a study design. Furthermore, assessors of the clinical response to shunting were not blinded to the result of the amyloid PET, representing a potential source of bias.

All studies were small, yielding a total of only 38 patients. Therefore, each study was only powered to identify large effects. As such, differential effects on each component of the iNPH clinical triad could not be assessed. Similarly, in such small cohorts, it was not possible to control for other factors associated with shunt responsiveness, such as age [11, 55], duration of symptoms [11, 56–58], gait disturbance predominance over cognitive impairment [10, 11, 57, 58], the presence of co-morbidities [55, 59], and the structural imaging features of iNPH and AD.

In the study by Leinonen *et al*, amyloid imaging was performed between 9 and 38 months after the biopsy and shunt insertion. This is problematic because the effects of shunting on amyloid PET is unknown. Secondly, since amyloid deposition is progressive, the amyloid PET is likely to be an overestimate of the amyloid burden at the time the decision was taken to insert a shunt. Lastly, a significant interval between shunting and imaging may cause selection bias based on disease severity or, more significantly, the response to shunting.

In addition to these inherent weaknesses of the studies included in this pooled analysis, there was also significant variation between the studies in the clinical, radiological and non-radiological investigations performed, which has implications for pooling results.

Recruitment by Leinonen *et al* required only “enlarged ventricles” and any one of the iNPH clinical triad, whereas the other two studies also required sulcal effacement and two of the iNPH clinical triad. Leinonen *et al* performed 24-hour intracranial pressure (ICP) monitoring in all patients before consideration of shunt insertion; in this study, all but one patient responded to shunting. Rinne *et al* used ICP monitoring “if required”, although specific indications were not discussed. Hiraoka *et al* performed CSF tap testing. As inclusion criteria become less stringent, the pre-test probability for iNPH decreases and so does the expected response rate to shunting.

The method of assessing the clinical response to shunting was variable. Methods included the iNPHGS [60], the Black score [61] or a non-disclosed “clinical assessment”. Different methods are likely to influence the reported rate of shunt response, which has obvious implications when pooling results. Furthermore, the timing of the assessment ranged from 2 months to over 20 months. Clinical improvement may occur over many months, which is reflected in the ongoing changes in the parenchyma and CSF spares through the first postoperative year [62]. On the other hand, clinical improvements can be fleeting [63–65] and therefore follow-up of at least one year is often used in clinical trials [66]. In two of the studies, assessment was performed at three months or earlier. The value of a clinical improvement lasting three months is debatable, and, in many centres, this would be considered unsatisfactory.

Two different radiotracers were used in the three studies. Multiple radiotracers have been developed with differing pharmacokinetics although all are highly specific for A $\beta$  [67] and correlation between radiotracer uptake is high [68–70]. Therefore, the diagnostic accuracy of different amyloid-specific radiotracers, and hence their role in patient selection for shunt insertion, is likely to be comparable.

## Reasons for lack of association between amyloid PET and shunt response

Firstly, amyloid PET may accumulate in the brain for reasons that have no effect on shunt response. While A $\beta$  deposition, alongside hyperphosphorylated tau protein, is a histopathological hallmark of AD [71], it is also observed in other neurodegenerative conditions such as Lewy Body Dementia [72, 73] and cerebral amyloid angiopathy [74]. Amyloid deposition also occurs in healthy aging [75–77], albeit with an increased risk of subsequent cognitive decline [78, 79]. Secondly, the potential for improvement post-shunting will depend on the degree of permanent neurological damage caused by NPH or any other comorbid condition [80]. Thirdly, a recent study showed CSF biomarkers of AD were associated with a positive response to tap-test [25]. This observation raises the possibility of a so-called neurodegenerative NPH (that would be amyloid PET positive) that is separate from an idiopathic NPH. Despite the result of this pooled analysis, amyloid PET may still have a role in the wider workup of patients for shunt insertion, particularly in identifying dual pathology. Even if amyloid PET does not predict immediate shunt outcomes, cerebral amyloid is likely to influence long-term prognosis, which would be relevant when counselling patients on the expected risks and benefits of shunt insertion.

## Requirements for future study

There remains a need for a blinded and randomized study to definitively determine the role of qualitative and quantitative interpretation of amyloid PET in predicting shunt response in patients with suspected iNPH. The study should be adequately powered to assess for differential effects of each domain of iNPH and to control for disease severity and other clinical features associated with long-term shunt outcomes. The predictive power of amyloid PET should be compared with the features apparent on structural imaging and biomarkers from CSF analysis. Finally, adequate follow-up of at least a year is required due to the progressive nature of AD and the often-transient improvements experienced following shunting.

## Conclusion

This pooled analysis does not support the use of amyloid PET in the selection of patients with suspected iNPH for shunting. Amyloid PET may however remain a useful adjunct in the workup of these patients, specifically for informing longer term prognosis. There remains the need for higher quality prospective studies to more conclusively evaluate the role of amyloid PET in this complex patient group.

## Declarations

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data and materials

Not applicable.

## Competing interests

Nil.

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## Authors' contributions

Dermot H. Mallon	<b>Study design, statistical analysis, manuscript drafting, manuscript review and editing</b>
Paresh Malhotra	<b>Manuscript review and editing</b>
Mitesh Naik	<b>Manuscript drafting, manuscript review and editing</b>
Christopher Carswell*	<b>Study design, manuscript review and editing</b>
Zarni Win*	<b>Study design, manuscript review and editing</b>

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## Tables

**Table 1: Summary of studies included in the pooled analysis.**

Study	Year of publication	Country	Number of patients shunted (total in study)	Recruitment period	Age (SD)	Sex (M/F)	Diagnostic criteria for NPH	CSF diagnostic test prior to shunt	Cognitive impairment assessment	Intervention	Definition of response
Leinonen	2013	Finland	11 (15)	2007–2010 <sup>a</sup>	70 (4.6)	11/4	Age >50  At least 1 of NPH triad  “Enlarged ventricles” on CT or MRI  Transfrontal 24-hour ICP shunt recording	All had CSF tap test <b>and</b> 24h intraventricular pressure monitoring	MMSE	Shunt	Not stated in clinical assessments
Rinne	2014	Finland	17 (18) <sup>b</sup>	... <sup>c</sup>	67.9 (6.7)	11/7	Age >50  Enlarged ventricles with obliterated cerebral sulci  At least 2 of NPH triad	All had CSF tap test <b>or</b> 24h pressure recording ‘if required’	MMSE	Shunt	Neurological assessments based on Black  Response considered here at least “
Hiraoka	2015	Japan	10 (30)	2010–2013	77.9 (4.1)	4/6	Age >60  At least 2 of NPH triad  Enlarged ventricles with obliterated cerebral sulci  Normal CSF pressure and content  Positive results on CSF tap test  No other cause of symptoms of hydrocephalus	All had CSF tap test	iNPH grading scale	Shunt	Gait, u and c... meast were u althou extrac data v provid chang cognit scores

<sup>a</sup> Recruitment dates not stated in article. Full cohort from Leinonen *et al* (2010). Start of recruitment given as 2007, the year in which <sup>18</sup>F-flutemetamol was developed. <sup>b</sup> 17 patients followed up due to patient death for cause unrelated to shunting. <sup>c</sup> Recruitment dates not stated in article.

Table 2: Technical detail of the amyloid PET scan.

Study	Radiotracer	Dose (MBq)	Uptake time	Acquisition time	Amyloid PET assessment
Leinonen	<sup>18</sup> F-flutemetamol <sup>a</sup>	174 (SD 3.4)	90	30	Qualitative
Rinne	<sup>18</sup> F-flutemetamol	176 (range 169-184)	90	30	Qualitative
Hiraoka	<sup>11</sup> C-BF227	. <sup>b</sup>	90	60 (dynamic acquisition)	Quantitative <sup>c</sup>

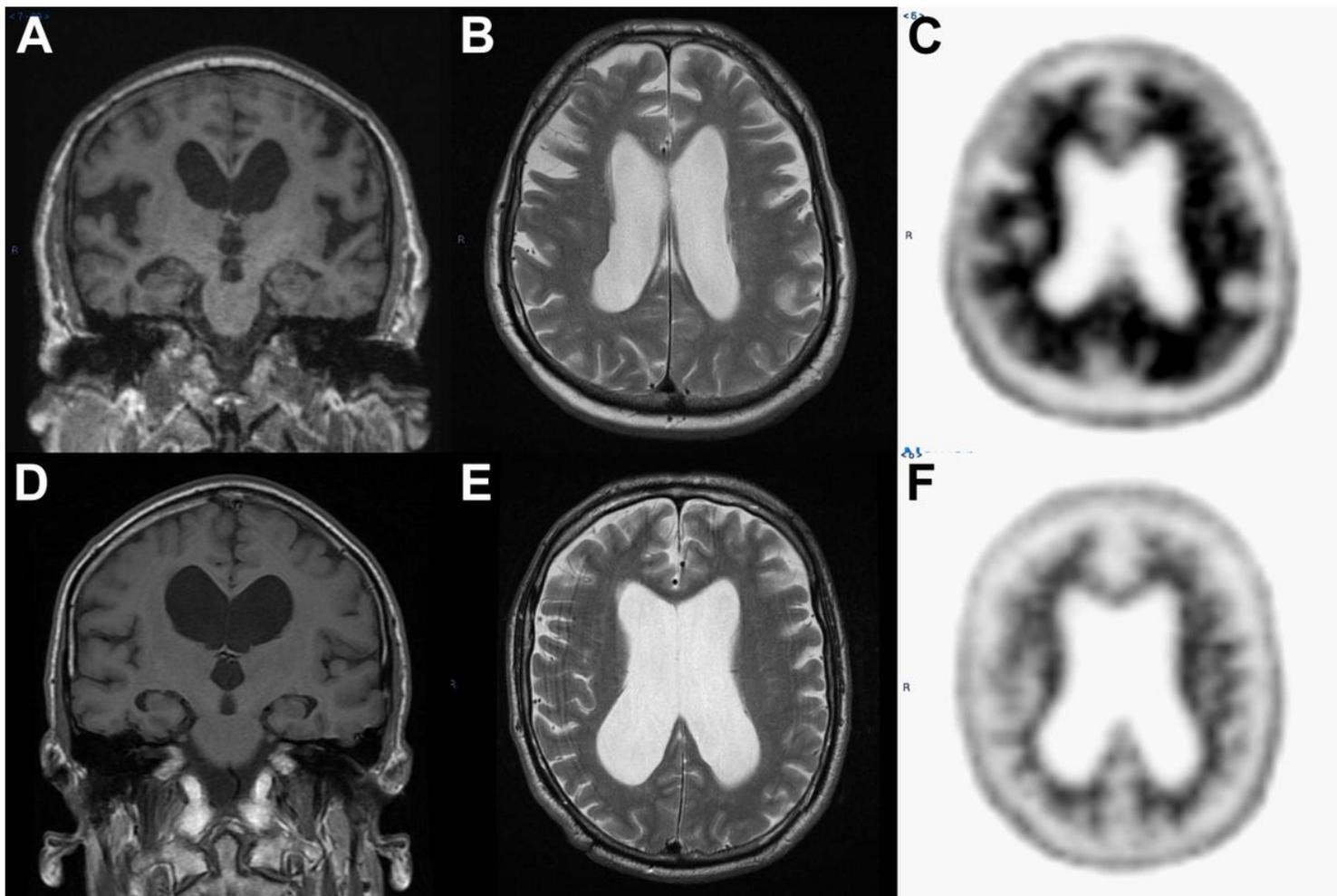
<sup>a</sup> <sup>18</sup>F-flutemetamol was used in all patients and therefore the results of this were used to calculate diagnostic statistics; PiB (C11) was used in a subset of 7 patients. <sup>b</sup> Radiation dose not provided. <sup>c</sup> SUVR of 1.15 was defined by lowest SUVR value within a confirmed AD group.

Table 3: Pooled diagnostic accuracy of Amyloid PET identifying patients that do not have a clinical response to shunting.

Study	Amyloid PET positive		Amyloid PET negative		<i>p</i> <sup>a</sup>	Sensitivity	Specificity	PPV	NPV	Accuracy
	No shunt response (TP)	Shunt response (FP)	No shunt response (FN)	Shunt response (TN)						
Leinonen	0	2	1	8	1.000	0.0 (0.0–97.5)	80.0 (44.4–97.5)	-	88.9 (85.4–91.6)	72.7 (39.0–94.0)
Rinne	2	1	7	7	1.000	22.2 (2.8–60.0)	87.5 (47.4–99.7)	66.7 (18.1–94.8)	50.0 (39.3–60.7)	52.9 (27.8–77.0)
Hiraoka	3	2	2	3	1.000	60.0 (14.7–94.7)	60.0 (14.7–94.7)	60.0 (29.2–84.5)	60.0 (29.2–84.5)	60.0 (26.2–87.8)
Pooled	5	5	10	18	0.473	33.3 (11.8–61.6)	78.3 (56.3–92.5)	50.0 (25.8–74.2)	64.3 (54.2–73.2)	60.5 (43.4–76.0)

<sup>a</sup> Fisher's exact test.

## Figures



**Figure 1**

Imaging features of normal pressure hydrocephalus and Alzheimer's disease. In a 70-year-old patient who presenting with cognitive decline, the coronal T1-weighted imaging (A) and axial T2-weighted MR imaging (B), suggested normal pressure hydrocephalus due to ventriculomegaly and crowding near the vertex. However, the 18F-florbetapir PET imaging (C) showed generalised increased grey matter uptake with loss of grey-white matter differentiation, particularly within the bilateral posterior parietal cortices. This signified extensive amyloid deposition prompting a diagnosis of Alzheimer's disease. Conversely, in a 67-year-old patient also with ventriculomegaly on MR imaging (D, E), the 18F-florbetapir PET imaging showed a normal pattern of uptake and preserved grey-white matter differentiation indicating no significant amyloid deposition. This patient had a significant and sustained response to shunting.

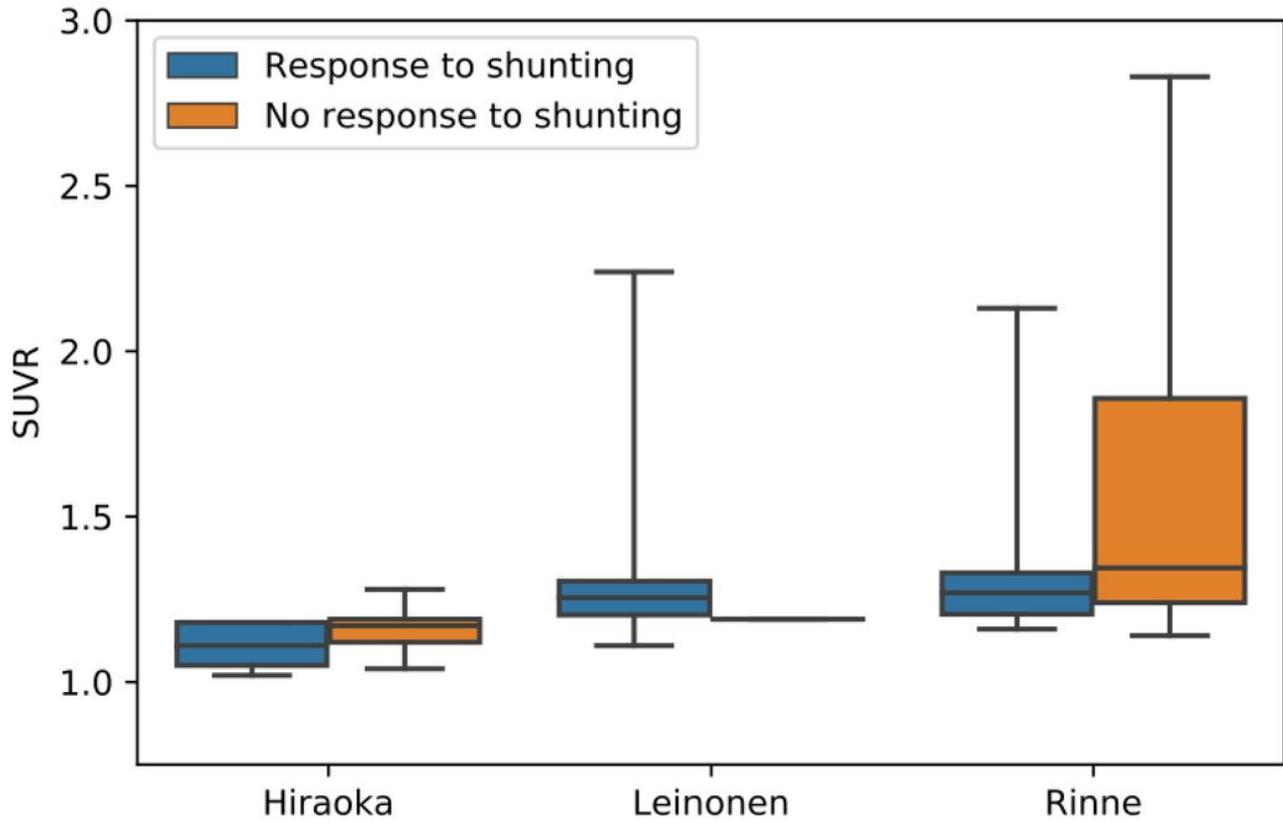


Figure 2

Box and whisker plot of SUVR values for patients with and without a response to shunting.

### Supplementary Files

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